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ERRATA : to be pasted page 28. Vol. 5 (January, 1943)

Page 28—

Line 8. *For* " (30) " *read* " (20) ".

Line 11. *For* " Fig. 2B " *read* " Fig. 3B ".

Page 29. Legend to Fig. 3, line 6. *For* " a 1 " *read* " an 11 ".

Page 30. Line 12. *For* " true " *read* " large ".

Page 31—

Line 7. *For* " is " *read* " was ".

Line 15. *For* " and " *read* " or ".

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21. (1942). *Amer. Heart J.*, **24**, 627.

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Addendum

While this article was in press, Schwartz and Marcus (Schwartz, S. P., and Marcus, H. (1942) *Amer. Rev. Tuberc.*, **46**, 35) reported a number of cases of our Type IV and several of our Type VI pattern. These patterns occurred predominantly in cases of chronic cor pulmonale. From their autopsy data in 7 such cases, as well as in 2 additional cases of congenital heart disease, the patterns appear to be most commonly associated with predominant hypertrophy of the right ventricle. However, they also occurred in the absence of ventricular hypertrophy when the right ventricle was dilated.

BACTERIAL ANEURYSM

BY

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Received January 22, 1943

Stengel and Wolferth (1923) made an extensive review of the literature of mycotic or bacterial aneurysms. Since that time a number of cases have been recorded presenting unusual clinical or pathological features. Three new cases are described in the present paper, and, at the same time, nineteen cases reported since 1923 have been analysed.

Pathology

Most of the earlier theories as to the causation of bacterial aneurysms—a term that is preferable to mycotic which suggests a fungoid infection—laid emphasis on the mechanical production of this condition. Ponfick (1873) thought that the aneurysm was due to an embolus containing a spine of calcareous deposit which secured penetration of the vessel wall and allowed the entry of bacteria: no further evidence has been adduced to support this view. It was also suggested that, whilst embolism was the commonest cause, the aneurysm was produced by the mechanical effects of the embolus at the site of obstruction. Goodhart (1877) first advanced the hypothesis that infective processes were concerned. Since Eppinger's work (1887), it has been generally conceded that the aneurysm forms as a result of the bacterial infection of the vessel wall carried by the embolus, and is therefore more likely to occur in bacterial endocarditis and other septic conditions in which the emboli are heavily charged with bacteria. Emboli from infected valves tend to lodge, as Eppinger pointed out, at mechanical turns or sudden narrowings of the vessels. In smaller vessels it is reasonable to suppose, and has been demonstrated, that the embolus may be sufficiently large to block the vessel directly. Aneurysms in such cases are not very common because the blood ceases to pound against the damaged vascular wall. When a large vessel is affected, as in Case I of this paper, it is probable that the embolus lodges in the vasa vasorum, causing an area of infection and weakening at this point; the vessel is not obstructed and the arterial pressure rapidly produces an aneurysm in the weakened area. Usually it is not possible to identify the embolus or even the affected area post-mortem, owing to the rapid changes taking place in the vessel wall and the tendency to perforation with the formation of a false aneurysm, but there are well-established cases in which the embolus has been recognized. Eppinger found the same organisms present in the wall of the aneurysm and in the vegetations on the heart valves. In a more recent case, Lippincott (1940) identified cocci in the vasa vasorum in a case of aortic bacterial aneurysm. More rarely a bacterial aneurysm develops as a result of direct spread, along the intima of the vessel wall, of infection from neighbouring foci. A good example of this is seen in the development of aortic aneurysms arising from contiguous aortic valve lesions. Still less frequently aneurysms result from periarteritis, the arterial wall becoming infected from some external focus. Probably some such state of affairs prevails in the vessels in areas of tuberculous lung infiltration and is eventually responsible for the hæmorrhage.

In the present analysis of 22 cases, 13 showed positive signs of bacterial endocarditis.

The origin of the others was varied. Lippincott's case was associated with pneumonia, septicæmia, and septic arthritis. Aschner (1932) recorded one in which an aneurysm of the aorta resulted from an infective arteritis of uncertain origin; this was thought to be due to "metastatic ulcerous aortitis" and a gonococcus was isolated from a blood culture. In two cases the aneurysm was associated with a septicæmia of uncertain origin, and in another (Crane, 1937) sepsis of the foot appeared to be the focus of infection. In two cases trauma seems to have played a part. In one, recorded by Bain and Wray (1941), there was a suggestion of trauma resulting in rupture of the aortic valve, and this was followed by bacterial endocarditis causing an aneurysm from the base of the ruptured valve: the case might well be used as an example of aneurysm from spread of contiguous infection. In the second case (Taylor and Reinhardt, 1939) both sepsis and trauma were concerned; the aneurysm was in the right common iliac artery and developed as a result of pyonephrosis in association with the trauma of ureteric catheterisation.

Size.—The size of the aneurysm was often unrecorded, but when details were available the tumour rarely reached any considerable size unless by perforation it formed a false aneurysm. Such was the case in the writer's example of aneurysm of the femoral artery which attained proportions of 3–4 in. in length and 1·5 in. in diameter. Most bacterial aneurysms are not more than a few cubic centimetres in capacity. A remarkable exception was recorded by Mims Gage, an aneurysm of the common iliac artery reaching the size of a grape-fruit and being ligated during a period of bacteriological recovery.

Bacteriology.—Where a causal organism has been identified it was usually a streptococcus, as would be expected from the frequent association of bacterial aneurysms with infective endocarditis. Amongst rarer organisms, gonococci and typhoid and anthrax bacilli have been mentioned. In recording his gonococcal case, Aschner mentions that seven others had previously been described. A case of particular interest is that of Knighton (1937–8) in which the identified organism was *Bacillus abortùs* causing a septicæmia with doubtful bacterial endocarditis.

Vessels Affected.—The site of bacterial aneurysm was stated by Stengel and Wolferth to be (in order of frequency) the aorta, abdominal arteries (superior mesenteric, splenic, and hepatic), and the cerebral and limb vessels. Mims Gage (1934) puts them in the following order: aorta, cerebral vessels, superior mesenteric arteries, and peripheral arteries, stating that the larger branches of the aorta are seldom involved. In the smaller series dealt with here, the aorta was again the most frequently affected. In 22 cases 8 involved the aorta, 3 the pulmonary artery, 2 the radial, 2 the common iliac, 2 the middle cerebral, 3 the mesenteric, 1 the popliteal, 1 the posterior tibial, 1 the femoral, 1 the axillary, and 1 the mitral valve. Often aneurysms occurred in more than one vessel, though this does not appear to be so frequent as is suggested by Eppinger. Prior to 1923, the number of cases of bacterial aneurysm of the pulmonary artery was comparatively small (in Stengel and Wolferth's series 14 out of 217 cases) and it is of interest to note that in this small series there is a relatively high incidence.

Associated Lesions.—The majority of aneurysms previously recorded seem to have been associated with common valvular lesions due to bacterial endocarditis. Amongst the 22 cases analysed here there was rather a high incidence of congenital defects, namely, 5 cases, including 1 of cor triloculare, 2 of coarctation of the aorta, and 1 of hypoplasia of the aorta. Two cases (one with coarctation) were suffering from patent ductus arteriosus. Probably these cases give a false impression of the frequency of congenital lesions as they were no doubt published partly on account of their rarity.

Clinical Manifestations

Age and Sex.—In the present series the average age was only a trifle higher than previously recorded, namely 33. Mims Gage (1934) states that most cases occur before the age of 30,

whilst Stengel and Wolferth showed the second, third, and fourth decades to be the commonest, as contrasted with the fifth decade, the commonest for syphilitic aneurysms. Males preponderated over females, as in the series analysed by Stengel and Wolferth.

Incidence.—Bacterial aneurysms are uncommon, though if detailed autopsies were possible in all cases of bacterial endocarditis, no doubt more would be found. Garland (1932) in 12,000 autopsies found 2·2 per cent of aneurysms, of which only 4 were bacterial in origin. In the examination of some recent records of bacterial endocarditis from the files of the Royal Infirmary and Smithdown Road Hospital, Liverpool, no case of bacterial aneurysm was found except those reported here.

Course.—Some attempt has been made to determine how long the aneurysms take to develop and the duration of life thereafter. This was not easy owing to the insidious and variable course of bacterial endocarditis. In most cases it would appear that the septicæmia was present for a few months before the aneurysm was detected, but that the aneurysm itself only took a few weeks (up to two months) to attain a recognizable size. Sometimes it was possible to date the beginnings of the aneurysm by a clear history of embolism. Once present, the course of the aneurysm was usually very rapid and death generally took place within six months. Not only do bacterial aneurysms seem to occur in the more severe cases of bacterial endocarditis, but in themselves constitute a complication of great gravity owing to the risk of rupture with hæmorrhage and of vascular obstruction in the case of limb vessels. Occasionally recovery takes place. In this series three cases are recorded in which the patient was still living at the time of publication. The case of Mims Gage has already been mentioned. Nicholson (1940) described a case of coarctation of the aorta in a child of 12 with arrested subacute bacterial endocarditis and a calcified bacterial aneurysm at the seat of stricture; treatment had only been symptomatic. In another case (Knighton 1937–38) there was a clear history of embolic obstruction in the right axillary artery occurring during the course of an abortus infection in which there was also aortic regurgitation and mitral disease; after the septicæmic symptoms subsided the aneurysm continued to enlarge but was dealt with by ligation. The heart lesions, of course, persisted, leaving the prognosis uncertain.

Diagnosis.—The diagnosis of bacterial aneurysms is often impossible especially in the case of deep-seated arteries. Aneurysms of the superficial arteries, open as they are to inspection and palpation, are more easily recognized and many more might be observed if careful observation of these vessels were made during the course of bacterial endocarditis. In the present series, 6 out of 7 peripheral aneurysms were recognized clinically. In the seventh an aneurysm of the radial artery was incised as an abscess (Areta, 1935). Of the aortic aneurysms only one was recognized, that recorded by Nicholson (1940) and already described: the diagnosis depended upon radiological identification of the calcified sac. In one of the original cases described by Stengel and Wolferth, the clinical diagnosis of a bacterial aneurysm of the aorta was made by the great pulsation in the upper chest and an increase in vascular dullness in a case of bacterial endocarditis. The possibility of embolic aneurysm of the cerebral vessels has sometimes been considered when localizing signs have pointed to a sudden vascular lesion of the brain during the course of bacterial endocarditis but confirmation is impossible. Such aneurysms frequently rupture so that to the embolic features there may be added symptoms due to cerebral hæmorrhage. This is illustrated by the case of Koch and Nuzun (1940) in which an aneurysm of the right middle cerebral artery resulted from embolism during a subacute bacterial endocarditis. Subarachnoid hæmorrhage or cerebral abscess was suspected from the physical signs and the presence of blood in the cerebro-spinal fluid supported the former diagnosis.

Embolism into the mesenteric vessels is notoriously difficult of diagnosis, usually suggesting some acute abdominal catastrophe, but the possibility should not be overlooked in view of the practical importance in saving the patient an unnecessary operation. In one of

the new cases recorded here the diagnosis was suspected whilst the patient was in hospital with bacterial endocarditis.

Treatment.—The treatment of bacterial endocarditis is most unsatisfactory even since the introduction of sulphonamide and allied therapy. It follows that bacterial aneurysms, commonly associated with bacterial endocarditis, are even less susceptible to treatment. In spite of this, out of 22 cases reviewed here, ligation of the aneurysms was possible in 2, in which the bacterial endocarditis was healed or apparently quiescent. It may be, therefore, that the development of sulphonamide therapy will lead to more cures of bacterial endocarditis and thus arrest the formation of aneurysms or permit of their surgical treatment if they develop. A great difficulty will always be the rapid development of the aneurysm to the point of rupture.

Notes of Three Cases

Case 1.—*Femoral Aneurysm.*

Admitted 1/9/1941 with history of pulsating swelling in left groin noticed the day before, preceded by soreness for one week. Rheumatic fever when aged 13 with occasional tonsillitis. Father said to have died from bursting of an aneurysm, ? aortic.

Condition on admission. Aged 35. General condition poor. Remittent pyrexia. Numerous petechiæ. No splenic enlargement. Heart: well marked aortic regurgitation. Urine: some red blood corpuscles and leucocytes. Sedimentation rate: rapid fall. Blood count: R.B.C., 3,200,000;

Fig. 1.—Case 1. Photograph, taken during life, showing the femoral aneurysm.

W.B.C., 9,000; Hb., 50 per cent. Gonococcal complement fixation test, positive. W.R., negative. Blood cultures, sterile. A diagnosis of bacterial endocarditis with bacterial aneurysm of the femoral artery was made.

On 19/9/1941, patient mentally confused, emaciated, and pale. Extensive purpura mainly of the trunk but including eyelid conjunctiva. Rough aortic systolic murmur with thrill, in addition to diastolic murmur of regurgitation previously found. Aneurysm larger. Loud rasping systolic murmur with thrill over the sac. Systolic and diastolic murmurs just above sac in the groin.

The patient died on 27/9/1941.

Post-mortem report. (Dr. C. V. Harrison.)

An emaciated man, rather pale, with innumerable petechial hæmorrhages about 3 mm. diam. scattered over body, especially over trunk. In the upper part of Scarpa's triangle on the left there is an ovoid swelling about 5 × 7 cm. (Fig. 1). Rigor mortis incomplete.

Cardiovascular System. Pericardium contained an excess of clear fluid. Heart slightly hypertrophied, 13½ oz. (364 g.). Tricuspid and pulmonary valves normal. Mitral valve, old rheumatic fibrosis and slightly stenosed (admits one finger). Infective endocarditis in the form of relatively flat warty vegetations, which have begun to spread on to the posterior auricular wall. Aortic valve also old rheumatic fibrosis and infective endocarditis similar to mitral; vegetations have spread

FIG. 2.—Case 1. The heart, showing vegetations on the aortic and mitral valves, due to acute bacterial endocarditis.

down on to the upper part of the interventricular septum and also on to the aortic aspect of the aortic cusp of the mitral valve. Myocardium of left ventricle, minute points of fibrosis up to 1 mm. diameter. Coronary arteries normal. Aorta, early atheroma.

Respiratory System. Each pleura contains about 200 c.c. of clear fluid. Both lungs show œdema and there is a little early broncho-pneumonia in the upper part of the lower lobe of the left lung.

Spleen. About normal size. About two-thirds of it substance infarcted, the infarcts being large and starting to break down in the centres (Fig. 3).

Kidneys. Both show a number of infarcts. Some small and fibrosing, others larger (up to 1·5 cm.) and recent. The right shows splotchy congestion, the left does not.

Ureters, bladder, etc., normal.

Alimentary tract and pancreas, normal. Liver, some acute congestion.

In the *left groin* there is an aneurysm of the left femoral artery arising just below Poupart's ligament. This is about $5 \times 5 \times 7$ cm. The anterior crural nerve is splayed out over it (Fig. 4). Apparently the aneurysm has either burst or leaked posteriorly because blood is ploughing up the muscles.

The specimen was dissected out en bloc and left to fix before opening.

Summary of Lesions. (1) Infective endocarditis superimposed on old rheumatic fibrosis of aortic and mitral valves. (2) Mycotic aneurysm of left femoral artery. (3) Infarcts of spleen and kidneys. Further dissection of the aneurysm after fixation showed that it had burst and that the wall of the

FIG. 3.—Case 1. Spleen showing numerous infarcts.

FIG. 4.—Photograph of aneurysm after dissection. Shows anterior crural nerve splayed over the mass which is chiefly due to a " false " aneurysm from leaking of original sac.

sac was now formed by the adjacent muscles. No remnants of the artery wall being visible in the parts examined.

Case 2. *Radial Aneurysm.* (Dr. Norman Capon's case.)

Man, aged 42. Symptoms for about three months. Anorexia, sweating, pain in the joints, fever for probably about two months.

On 7/9/1934 very severe pain in left forearm, with nothing to show for it.

On 13/9/1934 admitted to hospital. Mitral presystolic murmur. Petechial hæmorrhages. Negative blood culture. No splenic enlargement.

On 19/10/1934. Small aneurysm on front of left forearm. Blood culture repeated—negative. Patient left hospital at own request.

On 29/1/1935 the patient died at home. Dr. Rowlands reports that he became progressively weaker and finally had convulsions, ? due to intracranial embolus.

Case 3. *Mesenteric Aneurysm.*

Present History. A male, aged 23, working long hours as a clerk, was admitted on 11/12/1942. Rheumatic fever, when 7 (many weeks in bed), when 14, and again when 15. One attack since.

Tired and run down for past two months. Fleeting rheumatic pains a month ago. Red painful patches on the finger pads lasting a few days. Dr. Edwards noted fever a month ago and has kept him in bed since. Drenching night sweats, increasing pallor.

Severe abdominal pains since this morning. Vomiting, no blood. No diarrhœa or melæna.

On examination. Marked pallor. No finger clubbing, no petechiæ. Pulse rate, 110. Apex beat two inches outside nipple line; forcible. Blowing aortic diastolic murmur. Diffuse abdominal tenderness and rigidity.

Urine. A small amount of albumen; a moderate number of squamous cells, fair number of red cells, an occasional leucocyte, and a small number of cocci.

Clinical Diagnosis. Subacute bacterial endocarditis; mesenteric embolism.

On 14/12/1942 at 10 p.m. he was comfortable and had improved since admission. At 11.15 p.m. he collapsed. When seen, comatose with stertorous breathing and profuse sweating. His blood count showed 35 per cent hæmoglobin with a well-marked polymorphonuclear leucocytosis (polymorphs, 82 per cent; total leucocytes, 43,600).

He died at 1.20 a.m. the following morning.

Post-mortem report. (Dr. C. V. Harrison.)

Subacute infective endocarditis. Old rheumatic endocarditis. Mycotic aneurysm of mesenteric artery. Hæmoperitoneum. Very pale. Rigor mortis present. Abdomen rather full. No other lesion.

Abdominal cavity: Distended with enormous quantities of fresh blood.

Heart: Right side normal. Mitral valve thickening but no shortening. No stenosis or apparent incompetence. Slight thickening of posterior auricular wall. Left ventricle hypertrophied and dilated. Aortic valve old rheumatism and infective endocarditis, the latter on the aortic aspect of the aortic cusp of the mitral and the adjacent cusp of the aortic. It took the form of an ovoid, almost "puff ball" thrombus attached to the aortic valve with granular vegetations adjacent to it.

Blood vessels: There was an embolus in one of the main branches of the mesenteric artery. This had caused a mycotic aneurysm in the mesentery corresponding to the last two feet of small intestine. This had burst on its posterior aspect with a massive hæmorrhage.

Small intestines: Normal in spite of the aneurysm of the mesenteric artery. Stomach, colon, and appendix: normal.

Spleen: Shows a reaction in the form of a pale cellular pulp with not much softening.

Kidneys: Right kidney showed one healing infarct and a few minute petechiæ. Left kidney showed a few petechiæ. Ureters, bladder, and prostate, normal.

Summary

Three new cases of bacterial aneurysm are described, one of the femoral artery, one probably of the radial artery, and one of the mesenteric artery. The last ruptured, causing death from hæmorrhage into the peritoneal sac. The post-mortem findings are recorded in two cases.

Another nineteen cases have been collected, cases reported since 1923 when the subject was fully dealt with by Stengel and Wolferth. These have been analysed.

I am indebted to Dr. J. P. Steel for access to Case 1 and to the case sheets of Smithdown Road Hospital in search for further aneurysms. Professor Henry Cohen also allowed me to scrutinize his notes of recent cases of bacterial endocarditis. Dr. Capon kindly supplied the notes for Case 2 and Dr. G. Sanderson those for Case 3. Dr. C. V. Harrison performed the post-mortem examinations on Cases 1 and 3.

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HEART CHANGES IN ALKALOSIS

BY

J. STEWART LAWRENCE AND E. N. ALLOTT

Received March 11, 1943

Electrocardiographic findings in alkalosis were first noted in 1922 by Carter and Andrus, who observed that the Q–T interval was prolonged by more than 30 per cent in three of their cases; this was associated with a lowering of the blood calcium. Barker, Arbor, Shrader, and Ronzoni (1939) produced artificial alkalosis by voluntary overventilation or by ingestion of sodium bicarbonate, the Q–T interval being slightly increased by the latter procedure. In a hysterical patient with hyperventilation a similar effect was produced, but this did not exceed normal limits; a reduction of the T wave was also observed.

An opportunity occurred recently of studying the cardiac function in alkalosis.

Case Report

A woman of 47 was admitted to St. Nicholas Hospital on December 4, 1941. She stated that she had been well till three years previously when she began to suffer from occasional vomiting after meals and during the night. Abdominal pain was troublesome at times and was relieved by vomiting or alkalis. Since then she had never been free from the trouble for more than a day at a time. For the few weeks before admission the severity of the attacks increased and she took MacLean's powder frequently. On the day before admission she suddenly felt as though about to die and her hands and arms went into spasms and felt numb and tingling. This soon passed off, but returned the following morning. On admission, both arms were found to be in tonic spasm with elbows and wrists flexed, fingers and thumb in the position of *main d'accoucheur*. The abdomen was held tense. Blood taken at this time had a bicarbonate content of 150 vol., a blood urea of 132 mg., and a serum calcium of 10·2 mg., each per 100 c.c. Next day she became confused, disorientated in time, suspicious, and apprehensive. At this time she was having repeated cramps in her limbs and her tongue was dry and thickly coated. After administration of 5 c.c. of 5 per cent calcium chloride intravenously, she improved considerably.

On the third day in hospital she was again restless and confused, and kept trying to get out of bed with the intention of going home. Every piece of paper she could lay hands on (including her case notes) she would fold up and put in her bag. During the course of the morning she vomited three pints of greenish fluid. On examination she was found to be very emaciated, but had a good colour. The Chvostek sign was negative, Trouseau faintly positive. The blood pressure was 100/60. The heart was regular at a rate of 75; the two sounds were unusually close together but the apex beat was not displaced. The abdomen showed marked peristalsis, apparently gastric in origin, over almost its entire extent, and splashing could be elicited over a wide area. The temperature was 98·8°, respirations 22. The urine was neutral and contained much albumin. A cardiogram showed low voltage complexes in lead I and a greatly prolonged Q–T interval (0·56 sec.).

The serum bicarbonate at this time was 150 vol., chloride 166 mg., sodium 320 mg., and blood urea 310 mg., each per 100 c.c.; the B.S.R. was 52 mm. in the first hour and the circulation time (arm to tongue) 30 seconds.

An intravenous drip of 2 per cent saline at 120 drops a minute and stomach wash outs with saline were started. Improvement was rapid and by the fifth day the patient was normal mentally and less dehydrated in appearance. The serum bicarbonate had now fallen to 135 vol. and the chloride risen to 282 mg. and the blood urea was 210 mg., each per 100 c.c. A barium meal showed a large stomach with increased peristalsis, with obstruction at the pylorus, and a small prepyloric ulcer. By the seventh day the serum bicarbonate was 125 vol., chloride 319 mg., sodium 305 mg., and urea 42 mg., each per 100 c.c. On the eighth day, laparotomy was performed by Mr. Martin under local anæsthesia and pentothal. There was much prepyloric scarring with no ascertainable patency from

FIG. 1.—Electrocardiogram showing prolongation of the Q–T interval (0·56 sec.). There are some extrinsic excursions, especially in lead II.

external tests. The stomach was enormously dilated. A gastro-enterostomy was performed. During the operation the pulse became very feeble, the veins in the neck engorged, and the breathing shallow and infrequent; cyanosis was present despite a very light stage of anæsthesia, but oxygen resulted in a rapid improvement which was maintained for the remainder of the operation. Despite continued administration of saline intravenously the patient died two days later. A post-mortem examination was refused.

DISCUSSION

Bazett (1920) was the first to use the electrocardiograph to study the duration of systole in relation to the heart rate. He measured the Q–T interval (from beginning of Q to end of T) in lead II in a number of normal men and women, expressing the result by the formula: duration of systole $=K\sqrt{\text{duration}}$ of cardiac cycle. K was found to average 0·37 in men and 0·40 in women, the limits being 0·36 to 0·48. An increase of the relative length of systole has been found in conditions associated with hypocalcæmia, notably hypoparathyroidism, and to a less extent in diabetic coma, rheumatic carditis, cardiac enlargement, heart block, and chronic nephritis, according to Graybiel and White (1941). Hypocalcæmia would also explain the changes noted in their cases of alkalosis by Carter and Andrus. In the present case the Q–T interval was 0·56 sec. and the cycle 0·8 sec., so that $K=0{\cdot}63$, a very considerable increase; so great in fact that systole is twice as long as diastole instead of shorter than it. This resulted in a reversal of the heart sounds, the second occurring just before the first. As a consequence of the short diastole and inadequate filling of the ventricles, the first sound was short and sharp like a normal second sound, and therefore readily mistaken for it. The apparent proximity of the two sounds is explained by the fact that diastole is actually shorter than normal systole, as shown by calculating K, using diastole instead of systole in Bazett's formula, when K is found to be 0·27 (normal systole 0·36–0·44). The blood calcium was normal in this case, but there may have been a diminution of diffusible calcium (as has been postulated to explain the occurrence of tetany in alkalosis). Dehydration was here a pronounced feature, as it is also in diabetic coma and at one stage of chronic nephritis, and these two conditions are sometimes associated with prolongation of systole. Bazett's formula was

therefore used to calculate K for two patients with dehydration but without alkalosis; normal figures were found.

From the slow circulation time and, at one stage, the raised venous pressure, it is evident that there was considerable impairment of cardiac function. Two factors were probably operative in its production. Firstly, the diastole was shortened, so that the great veins were not emptied completely before systole occurred. Secondly, the breathing was shallower and slower, due to the effect of alkalosis on the respiratory centre, so reducing the normal pumping action of the respiratory movements, particularly when, during the operation the respirations were further depressed by the anæsthetic.

Summary

The cardiographic findings in a severe case of alkalosis are described.

Marked prolongation of systole was present, so that systole came to be greater than diastole. This was associated with an alteration in the relationship of the heart sounds and impaired cardiac function.

The similarity to changes found in hypocalcæmia is discussed.

We wish to express our thanks to Dr. F. J. Power, Medical Superintendent of St. Nicholas Hospital, L.C.C., for facilities granted.

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EFFECTS OF PLASMOQUIN, ATEBRIN, AND QUININE ON THE ELECTROCARDIOGRAM

BY

H. L. HEIMANN AND B. G. SHAPIRO

From the Oribi Military Hospital, South Africa

Received April 21, 1943

Our attention was drawn to the changes in the electrocardiogram during the administration of plasmoquin, by the fact that leads IV R and IV F showed changes of the coronary type in a soldier, agend twenty-two, who complained of præcordial pain while receiving this drug. While we have seen several cases of indisputable coronary thrombosis in soldiers of about this age coming from the Middle East, the clinical picture in this man did not warrant the diagnosis. We were, therefore, led to wonder if the plasmoquine could not be responsible for this type of curve. As this patient had also had atebrin and quinine a short time previously, it was necessary to examine the effect of all these drugs on the cardiogram.

At this time, there were a number of men in the hospital who were convalescent from malaria and needed courses of these medicaments against relapses. They were in a reasonably good state of health as the malaria had been contracted six or more weeks previously, and they had been apyrexial for about four weeks. None were grossly anæmic, so no abnormal cardiographic findings were to be anticipated as a result of malaria itself at this stage of convalescence—if, indeed, malaria does cause such changes at any stage, and we have not found any reference to such changes.

A series of six men were first investigated. They had had various of these anti-malarial drugs in previous months. When the effect on the case mentioned above was noticed, cardiograms were taken in these six and they were then put on plasmoquine for one week (1/6 grain b.i.d.). At the end of this period a second cardiogram was taken. All drugs were then omitted for a week, when a third cardiogram was taken. They were then put on to atebrin 1·5 grains, t.i.d., for a week, and a fourth record was taken. As time was pressing, they were not given a rest period, but were immediately put on quinine for six days, the dose varying from 5 to 10 grains, t.i.d. A fifth record was then taken.

Owing to shortage of bromide paper, our observations were made principally on the chest leads, for in them the changes seemed most marked. Leads IV R and IV F were used, as defined by the joint British and American committees on præcordial leads.

Findings

Plasmoquin

P wave. There was some increase in amplitude, mainly in lead IV R.

P–R interval. No effect was observed.

QRS wave. The effect was variable on Q, but generally there was an increase in amplitude in lead IV R and no effects in IV F. No definite effect on R was observed. The effect on S was variable and it was generally increased in amplitude, even up to double, in leads IV R and IV F.

T wave. This was increased in amplitude up to double in leads IV R and IV F.

S–T segment. In several cases this became elevated, sometimes being bowed with the convexity downwards (Fig. 1 A). These elevated curves simulate those of coronary thrombosis. Later the segment becomes a steep rising one to the increased T wave. (See Fig. 1 B).

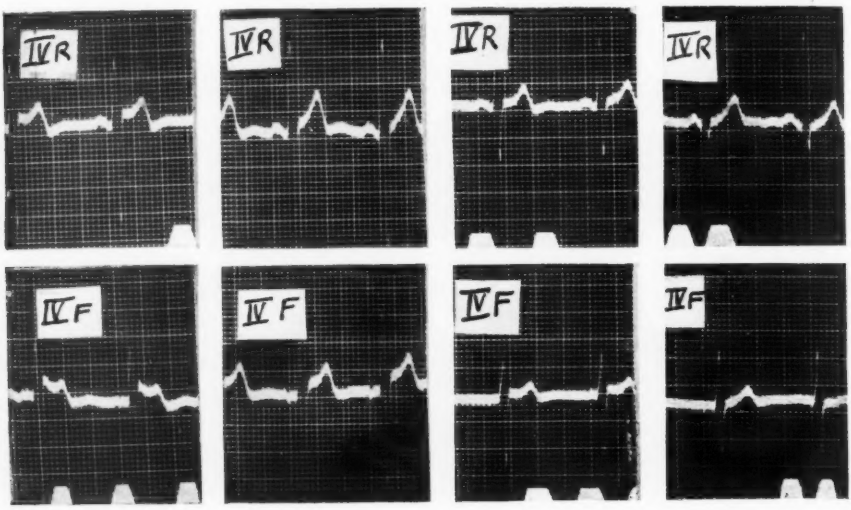

FIG. 1.
(A) Effect of plasmoquin on the electrocardiogram. The patient was taking 1/6 grain, b.i.d.
(B) Effect of plasmoquin, 1/6 grain, b.i.d., for 7 days.
(C) Effect of atebrin, 1·5 grains, b.i.d., for 7 days.
(D) Effect of quinine, 7 grains, b.i.d., for 5 days. All these figures are from the same patient.

Atebrin

P wave. This was generally decreased, sometimes to half the previous size in lead IV R.

P–R interval. This was unaffected.

QRS wave. The Q wave may be increased in amplitude; the R and S waves were generally decreased in amplitude.

T wave. This was markedly depressed in all cases, and sometimes in leads IV R and IV F, by as much as 70 per cent of normal (Fig. 1 C).

S–T segment. Atebrin restored this to iso-electric level after elevation by plasmoquin.

Quinine

P wave. This was decreased, but not to the extent seen in the atebrin effect.

P–R interval. No effect.

QRS and S–T. There was no constant effect on Q or on the S–T segment, but R and S were decreased in amplitude in both IV R and IV F (Fig. 1 D).

T wave. This was markedly decreased, though less than by atebrin. Often a small negative phase followed the initial positive phase.

SUMMARY

The effects of plasmoquin, atebrin, and quinine on the electrocardiogram of convalescent malarial patients has been investigated.

Plasmoquin increases the amplitude of the various deflections, affecting the T wave most

markedly and constantly. In some cases the most striking feature is the effect on the S–T segment which simulates the cardiogram of coronary thrombosis. Whether this is due to an effect on the coronary circulation, we are not in a position to state.

Atebrin decreases the amplitude of the various deflections, also affecting the T wave most markedly and constantly. It restores the S–T segment to the iso-electric level after it has been elevated by plasmoquin.

Quinine has an effect similar to atebrin but to a lesser degree.

Differentiation between the effects of plasmoquin on the one hand, and of atebrin and quinine on the other, in a particular patient may be made on the cardiographic findings given above. Plasmoquin increases the size of the T wave above normal while quinine and atebrin decreased it below normal. Plasmoquin often has an effect on the S–T segment, as described ; this is not seen in the exhibition of either of the other two drugs.

A CASE OF SUBENDOCARDIAL INFARCTION

BY

R. KEMBALL PRICE AND L. R. JANES

Received May 3, 1943

Disease of the coronary arteries, by commoner occurrence or by more frequent diagnosis, is assuming increasing importance in clinical medicine. The following case is reported because it shows some interesting features, and full clinical, cardiographic, and pathological investigation was possible.

A schoolmaster, aged 55, was admitted to hospital on November 16, 1941, with a three weeks' history of increasing angina of effort. Clinical examination showed nothing abnormal except a blood pressure, 155/100; W.R. negative. After admission to hospital he continued to have short attacks of pain relieved by amyl nitrite, after some of which T wave inversion in leads I and IV persisted for several days (Fig. 1). He was nervous and irritable, and attacks were usually precipitated by annoyance over some imagined grievance against other patients in the ward. Cardiograms taken during an attack on December 11 showed inversion of T IV, and 10 minutes after amyl nitrite, recovery of T IV to the upright position (Fig. 2). On December 20, the patient had a prolonged attack of pain not relieved by amyl nitrite, after which attack the cardiogram showed persistent T wave inversion in leads I and IV (Fig. 3).

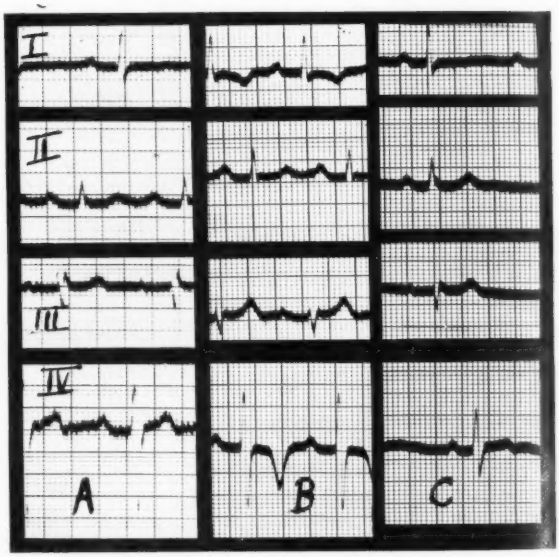

FIG. 1.—(A) Before attack (12.11.41). (B) Three days after attack of pain lasting 2 hours (17.11.41). (C) Return towards normal, 12 days later (29.11.41).

He made satisfactory progress and the blood pressure stabilized at about 150 mm. He started to get up on February 6, six weeks after his infarct.

Two days later, February 8, a severe attack of pain across the chest commenced at 6 a.m., and after failure to obtain relief from amyl nitrite, 1/4 grain of morphia was given and the dose repeated two hours later. At 11 a.m. he was seen by one of us (R. K. P.) and as he was still in great pain another quarter of a grain of morphia was given intravenously. This gave rapid relief and he was alseep within ten minutes. He woke again one and a half hours later and complained of pain and a further 1/4 grain of morphia was given subcutaneously. After this he remained comfortable.

An electrocardiogram taken the following day showed RS–T distortion with elevation

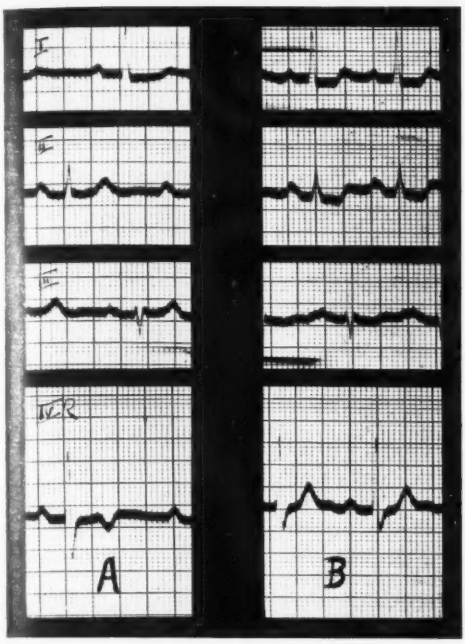

FIG. 2.—(A) During an attack of pain. (B) Ten minutes later, after amyl nitrite (11/12/41).

in leads II and III, with inversion of T waves. His blood pressure remained low 90–100/70–80, and on February 14, six days later, he began to complain of shortness of breath. The quality of the heart sounds deteriorated and on February 16, gallop rhythm was heard at the apex and rales were detected at the bases of the lungs. The pulmonary œdema cleared temporarily after injections of neptal, but the patient's general condition became worse. On February 26, a blowing systolic murmur became audible at the apex and persisted. He developed acute pulmonary œdema on March 3, and died within a few minutes, three weeks after the second infarction.

SYNOPSIS OF AUTOPSY

The deceased was a heavily-built obese man. No œdema of the feet nor ascites was present. There was acute œdema of the lungs with 140 c.c. of non-fibrinous straw-coloured fluid in each pleural cavity. The liver showed early chronic venous congestion. The kidneys appeared normal. The pancreas was very fatty. A hydrocele of the left testis was present.

The heart was enlarged and weighed 567 g., due to left ventricular hypertrophy. Considerable pericardial fat covered the heart. There was no pericarditis or endocardial exudate. The aortic valve was competent but atheroma was present at the base of the mitral and aortic cusps. Considerable atheroma of the aortic arch and of much of abdominal aorta was found. Atheromatous fatty streaking of the pulmonary arteries and their main branches was present.

The main coronary arteries showed much atheroma but no actual occlusion. There was extreme atheromatous narrowing, one inch from the opening into the aorta, of the right coronary artery, and similar narrowing of the left coronary artery one-third of an inch from its origin.

Focal disseminated fibrosis was present in the left ventricular muscle in its left outer border throughout its length, and also in the anterior wall near the junction with the inter-ventricular septum in the proximal part of the left ventricle near the base of the heart.

There was a large "sheet-like" subendocardial infarct extending from the base of the left ventricle at the auriculo-ventricular ring to the apex, involving the posterior wall of the left ventricle including the posterior papillary muscle, and the interventricular septum throughout its length, and extending on to the anterior wall of the left

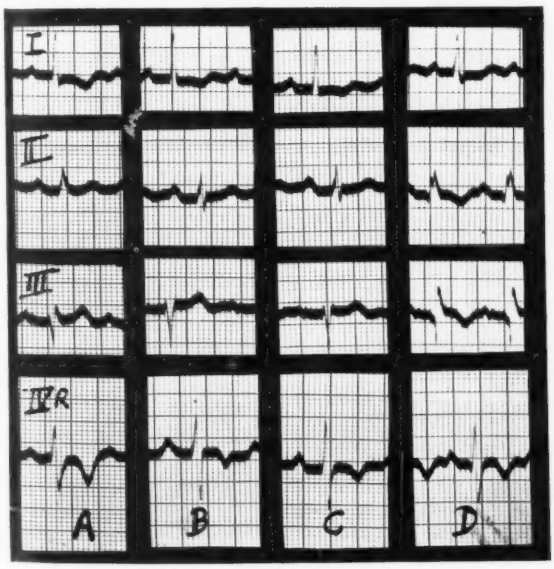

FIG. 3.—(A) Two days after prolonged attack of pain (22/12/41). (B) Before amyl nitrite (5/2/42). (C) After amyl nitrite (5/2/42). (D) One day after attack of pain lasting 5 hours (9/2/42).

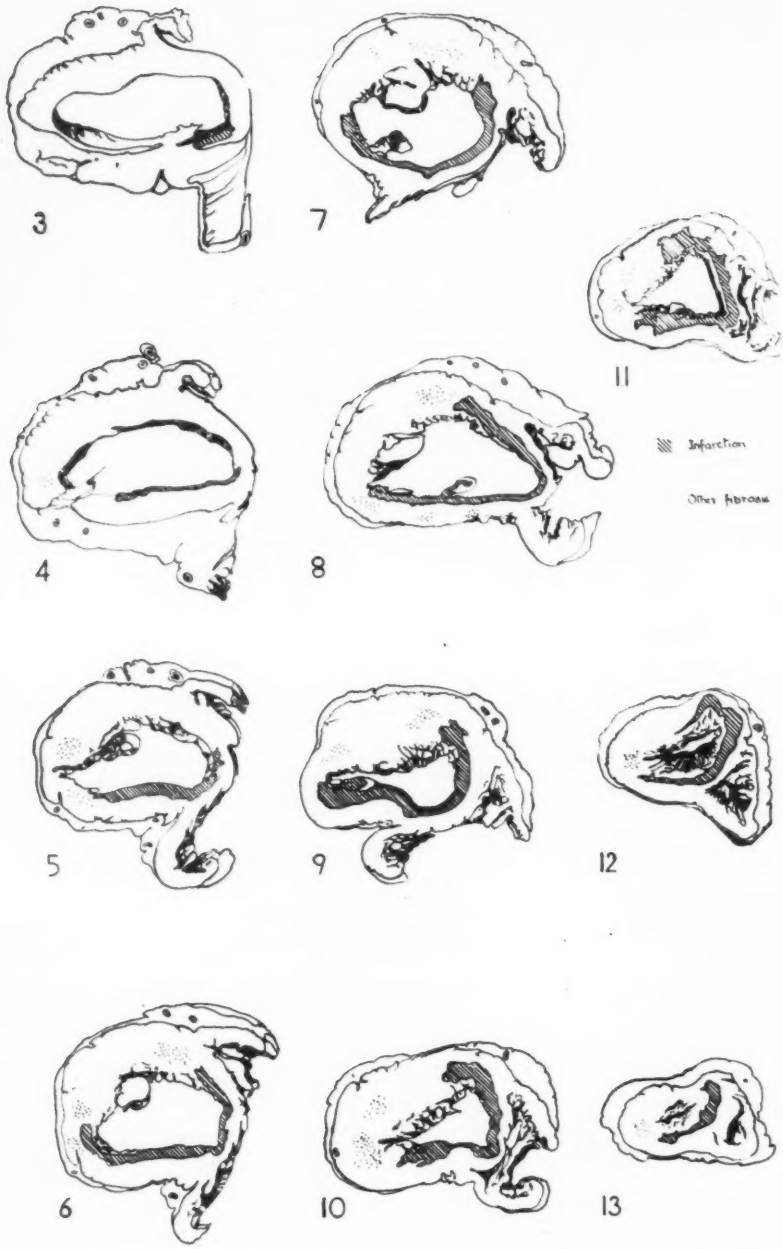

FIG. 4.—Photograph of a series of drawings of transverse sections through the ventricles, made at interval of approximately 5 mm., extending from the atrio-ventricular ring (No. 3) to the apex (No. 13). Th sheet-like recent infarct is shown cross-shaded ; the areas of focal fibrosis, as a series of dots.

ventricle in its middle and distal portions. Whereas the bulk of the infarct was subendocardial, this latter anterior portion moved away from the endocardium to lie intramurally.

This " sheet " infarct was of recent origin and was yellowish-red in colour. Its extent together with the areas of focal fibrosis are shown in Fig. 4. Comparison may be made with the distribution of the subendocardial fibres of the superficial bulbo-spiral muscle in Fig. 5.

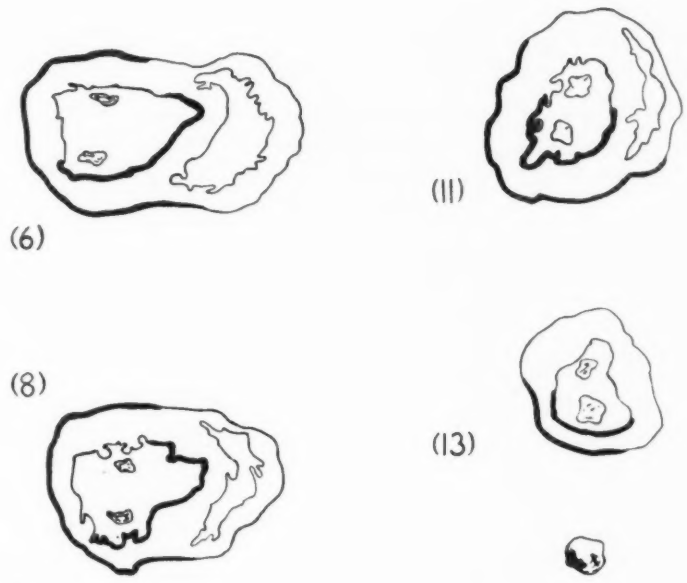

FIG. 5.—Photograph of a drawing to illustrate reconstruction of the superficial bulbo-spiral muscle. The numbers correspond approximately to the same level of transverse section as numbered in Fig. 4 [after T. E. Lowe (1939)].

DISCUSSION

A number of references to subendocardial infarction have been found. Parkinson and Bedford (1928) described occlusion of the circumflex branch giving rise to infarction of the lateral and posterior walls of the left ventricle usually involving the papillary muscles of the mitral valve. Whitten (1930) in an article on the relation of the distribution and structure of the coronary arteries to myocardial infarction mentioned one type of subendocardial infarct, which he suggested was due to occlusion of one or more of the large subendocardial branches that course often for a considerable distance in the subendocardial musculature, usually in relation to the columnæ carnæ or papillary muscles. Barnes and Ball (1932) investigated the incidence and situation of myocardial infarction in 1000 consecutive autopsies at the Mayo Clinic and found 49 cases, of which 28 were anterior apical, 24 posterior basal, 8 midventricular, and 3 diffusely beneath the endocardium; they state that in an occasional instance chronic infarction is diffuse, tends to extend in the form of subendocardial fibrosis and involves the entire left ventricle more or less completely. Lowe (1939) from a study of myocardial scars suggested a type of myocardial infarction that depends upon the interruption of the blood supply to a muscle bundle in the myocardium; this muscle bundle need not be supplied by a single main coronary vessel but may receive its blood supply from smaller branches of a number of vessels. In later articles, 1939 and 1941, he reported cases and attempted to correlate the clinical and cardiographic evidence with the post-mortem findings. Among the 5 new cases reported in 1941, Case 91 showed cardiographic changes consistent

with lesions of the superficial and deep bulbo-spiral muscles, and these findings were confirmed at autopsy. Robb and Robb (1939) have done experimental work on dogs and have also investigated a considerable number of human cases. They emphasize that the characteristic electrocardiogram appears, not in association with involvement of some one artery, not always in relation to the anterior or the posterior surface, but constantly in the presence of a lesion of the one muscle band. Blumgart *et al.* (1940) from an extensive investigation of pathological material conclude that the site of infarction bears no necessarily constant relationship to an occlusion of a coronary vessel. They stress the importance of the collateral circulation and describe a mechanism whereby fresh occlusion of the right coronary artery may cause infarction of the left ventricle, " infarction at a distance."

The infarct in the case now reported corresponds approximately to the area described for the subendocardial portion of the superficial bulbo-spiral muscle. Robb and Robb state that lesions of this muscle always cause RS–T depression in lead I and RS–T elevation in leads II and III. The direction of the T waves they regard as of less importance. Though all our electrocardiograms show this tendency, it is much more marked in Fig. 3 D where it is associated with T wave inversion in leads II and III.

It appears to us that in the case of infarcts in the less common situations the site of infarction is likely to be determined by a combination of three factors, the vessels occluded, the muscle bundle involved, and the state of the collateral circulation. We have been unable to find any reports of this possible " muscle bundle " localization in this country and for that reason feel that the report of a single case may be of interest.

Summary

A case of coronary arterial disease is described. It was observed to progress through the stages of angina pectoris, coronary insufficiency, and cardiac infarction to a fatal termination four months after the onset of symptoms. Detailed clinical and cardiographic evidence was obtained during life and a careful examination of the heart was made after death. A type of infarct is described that may correspond to a muscle grouping in the ventricle rather than to the distribution of a main coronary vessel.

We wish to thank Miss. J. D. Cross, of the Pathological Department, Royal Sussex County Hospital, for drawings from which photographic Fig. 4 and 5 were made.

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EXTREME CARDIAC HYPERTROPHY

REPORT OF TWO CASES WITH AORTIC HYPOPLASIA AND ENDOCRINE DISORDERS

BY

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From the Birmingham United Hospital

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Cardiac hypertrophy exceeding 1000 grams in weight is rare. Golden and Brams (1937) could only find 37 cases recorded, excluding the 9 that they themselves reported. They did not include in their survey the cases occurring in acromegaly, to which Courville and Mason (1938) drew attention. In the two cases here reported the hearts weighed 1350 and 900 grams respectively and were associated with aortic hypoplasia and disorders of the endocrine system, one having diabetes mellitus, the other an interauricular septal defect and acromegaly.

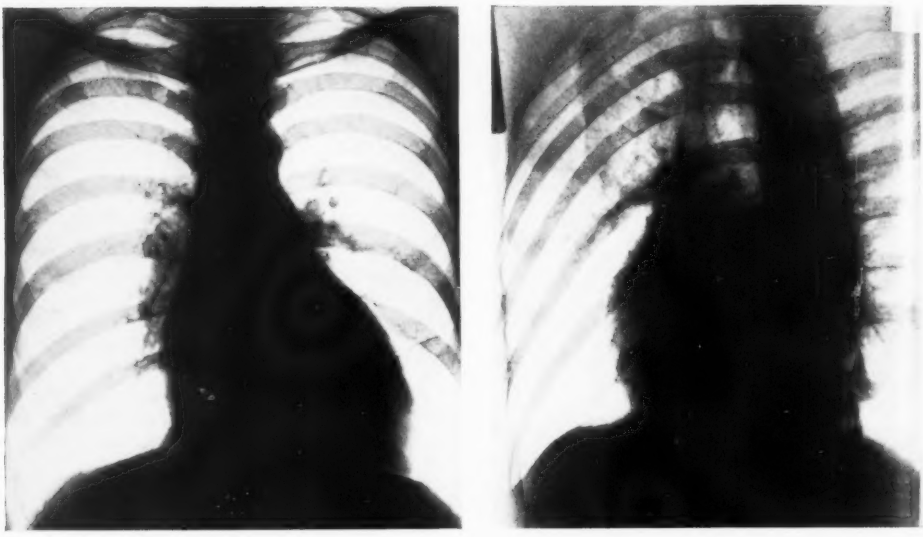
Notes of First Case

This man had suffered with chronic nasal infection for many years and in 1935 he underwent drainage of the left frontal sinus. In 1936, when 28 years old, he began to lose weight and to be extremely thirsty; diabetes mellitus was diagnosed. He was treated with 60 units of soluble insulin and a diet containing 90 g. of carbohydrate daily.

He first attended the diabetic clinic of the Birmingham United Hospital in November, 1937. The same dietary and insulin regime was continued. Physical examination at that time showed a well-built man, 5 ft. 10 in. tall and 141 lb. in weight. The heart was enlarged and there was a systolic murmur and thrill of moderate intensity, just internal to the apex beat. The rhythm was regular at a rate of 80–85 beats a minute and the blood pressure varied between 100/70 and 120/80. At the diabetic clinic his blood sugar rose to between 300 and 400 mg. per 100 c.c. after lunch, but in spite of this he felt well and was able to do heavy work as a foundry worker. Six months later, however, on the same dosage of insulin and diet he began to have frequent hypoglycæmic attacks and for the next six months he was stabilized with 30 units daily, but then the blood sugar levels again climbed to between 300–400 mg. per 100 c.c. with no obvious change in the patient's well being. In 1938 he was admitted to hospital on account of hypoglycæmic coma, and careful examination at that time suggested a diagnosis of interventricular septal defect. The electrocardiogram showed a normal P–R interval, marked left axis deviation, and inverted T waves in leads I and II. Radioscopy showed the transverse measurement of the heart was 16·5 cm., with a chest diameter of 29·5 cm. (Fig. 1). Physical examination did not show any change and the blood pressure still remained at the same level.

In July, 1940, he was again admitted for investigation. He was then complaining of marked weakness and inability to work over the previous five weeks. He had noted, also, profuse sweating even when at rest and some breathlessness and palpitations on exertion. Again, physical examination was essentially as before, his Wasserman was negative, while his basal metabolic rate was +28 per cent with a basal pulse rate of 88.

At this time he was taking 150 g. of carbohydrate and 25 units of soluble insulin twice a day. He was treated with rest in bed and improved rapidly. After this he gave up his job as a foundry worker and took on that of a bread salesman. In January, 1941, he was admitted with hyperglycæmic coma, which rapidly reacted to treatment, but from this time onwards he began to complain of general weakness, listlessness, profuse sweating, and some swelling of his ankles at nights. His diet had now been increased to 170 g. of carbohydrate daily and his insulin to 25 units twice daily. His symptoms were severe enough to cause him to stop work for 10 weeks and rest at home. This caused a good deal of improvement but a basic metabolic rate, as an out-patient, was shown to be +35 per cent and he was, therefore, admitted again for investigation on 21/1/41. At that time a note was made



A B

FIG. 1.

(A) 1938. Radiograph showing general enlargement of heart. In 1941 (one month prior to death) a radiograph showed no evidence of any increase in size since 1938.
(B) 1938. Left (II) oblique view showing left ventricular enlargement.

that his eyes were rather prominent and there was some clubbing of his fingers. Examination of the heart was as before with a blood pressure of 100/70. The thyroid gland was not enlarged or palpable. His basal metabolic rate was +48 per cent with a basal pulse rate of 92. On 17/5/41 he was first seen by us and a note was made: "Main complaint, loss of energy and marked sweating. On questioning, a cough for nearly two years with some sputum (this had been negative for tubercle bacilli in the past), never blood-stained. Weight constant. Some palpitation on exertion, no nervousness, fair appetite, had always had mild exophthalmos."

Examination showed no tremor but much sweating and marked nasal catarrh. No thyroid enlargement and no positive eye signs. Early clubbing of fingers. Heart enlarged. Moderate systolic murmur just internal to apex beat. Spleen not enlarged.

This time his metabolic rate was +60 per cent with a pulse rate of 80. X-ray of chest did not show any pulmonary infection and the heart shadow could be exactly superimposed on that taken in 1938. It was considered that surgery was not indicated at the time and observation was therefore continued and further attempts were made to control his diabetes and his excessive sweating. He was improving and the diabetes becoming more stable so that he was able to be about the ward helping with routine duties. A primary pituitary dysfunction explaining both the unstable diabetic state and thyrotoxic symptoms was considered possible. However, on 4/7/41 following seeing his visitors and being about to have his tea, with no symptoms of any sort, he went unconscious and died a few minutes later.

Post-mortem examination. This was carried out eighteen hours after death by Professor Haswell Wilson. The body was that of a well-developed man, with some lividity of the head, neck, and dependent parts.

The pericardial sac was normal. The heart (Fig. 2) was enormously enlarged, 1350 grams in weight. The left ventricle was hypertrophied, the wall measuring 5 cm. (after fixation in formalin). The right ventricle was also hypertrophied but to a much less extent, measuring 1 cm. in thickness. Both were slightly dilated with relative incompetence of the mitral and tricuspid valves. There was no ante-mortem thrombus. The coronary arteries were healthy in appearance but the solid mass of muscle showed areas of diffuse fibrosis, evidently a degenerative change supervening on extreme hypertrophy. There was no valvular lesion in the heart. The ascending aorta appeared to be of normal diameter at the aortic valves. The diameter gradually narrowed to a point just proximal to the attachment of the remnants of the ductus arteriosus. There did not appear to be any actual coarctation, the circumference at this point in the fixed specimen measured 5 cm. approximately. The distal part of the aorta tapered down gradually so that the circumference of the common iliacs

FIG. 2.—The interior of the left ventricle is shown. The great thickness of the wall and apparently normal aortic valves are seen. The right ventricle has also been opened and also shows hypertrophy (Case 1).

was only 2 cm. respectively. Extensive and severe atheroma was present in the lower part of the aorta and common iliac arteries, contrasting with the ascending aorta.

The lungs were voluminous and overlapped the pericardium. The left was adherent all over by old fibrous adhesions. The right was free. Both showed chronic bronchitis and emphysema, with sticky muco-pus in the bronchi and some œdema at the bases and posteriorly.

The peritoneum was normal. No abnormality was found in the abdominal organs. They were all engorged with blood. The pancreas showed no gross structural change.

The brain and its membranes were congested. The brain itself was rather atrophic with thin convolutions and wide perivascular spaces. The vessels at the base were healthy. No obvious lesion was found in the pituitary, thyroid, or suprarenals.

Histology. The heart muscle fibres were generally greatly hypertrophied although some were atrophic (Fig. 3). All sizes of fibres were present up to a diameter of 23μ. The nuclei were also markedly enlarged, appearing lobulated in many cases. Throughout the whole myocardium the interstitial fibrous tissue was increased and in some areas this was marked. There was no evidence of any inflammatory lesion. The arteries appeared normal though in several areas there seemed to be an increase in the perivascular lymphatic spaces of some arteries. There was no evidence of arteriosclerosis. Special stains did not reveal the presence of either amyloid or glycogen.

Sections from the thyroid and kidneys were entirely normal. Sections from the pituitary were not made.

Comment. This man was able to carry on heavy work as a foundry worker for at least two years with no increase in the radiological size of his heart. Only in the last year of his life did symptoms of diminished cardiac reserve appear. Moreover the measurement of the heart by X-ray examination gave us little indication of the excessive weight. The reason was obvious at autopsy when it was seen that the size of the heart chambers was small when compared with the muscle mass.

For some inexplicable reason the mode of death in gross enlargement of the heart is frequently sudden ; and pathological examination, as in this patient, is often unable to elucidate the actual cause.

NOTES OF SECOND CASE

A woman, aged 32, was admitted to the Birmingham United Hospital in August, 1939, for increasing shortness of breath and palpitation on exertion. She had been short of breath all her life, a

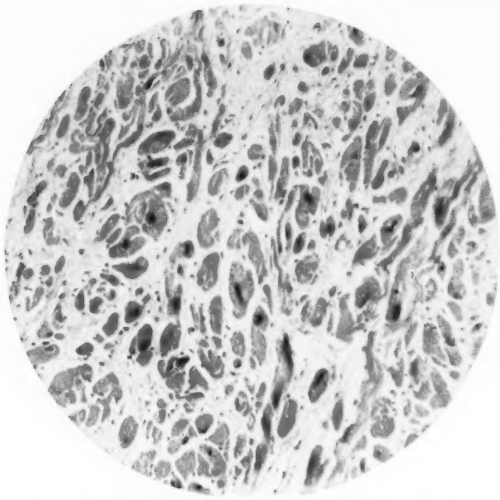


FIG. 3.—Photo-micrograph of ventricular wall showing the variation in size of muscle fibres and the increase of fibrous tissue. Magnification × 150 (Case 1).

fact she had attributed to a goitre. Her arms had always been hairy and her menstruation irregular. For ten years she had been taking thyroid tablets which caused her periods to become regular. Her weight had been constant at 165 lb. for many years. Recently her shortness of breath had become so marked that she was unable to do her housework and could only sit out of bed in a chair. Examination then showed a patient of masculine build, 5 ft. 8 in. tall, with a large head and hands and hairy arms and legs. The thyroid was enlarged, extending up from behind the sternum. There was no exophthalmos. The apex beat was outside the midclavicular line (Fig. 4): the heart was fibrillating

FIG. 4.—Radiograph of the chest (Case 2) showing the large retrosternal goitre, the enlarged heart, and th marked pulmonary vascular shadows, especially at the hila.

with a systolic and diastolic murmur at the mitral area heard all over the praecordium. The blood pressure was 130/80. There were no obvious clinical signs of congestive cardiac failure. The lungs, abdomen, and central nervous system did not show any abnormality. A cardiogram showed auricular fibrillation, rate 125, and left axis deviation.

An X-ray of the skull showed enlargement of the pituitary fossa. Her basal metabolic rate taken on five separate occasions varied between +21 and +28 per cent. A diurnal variation blood sugar curve showed values never rising above 100 mg. per 100 c.c. A diagnosis of acromegaly, retrosternal goitre, and rheumatic heart disease with mitral stenosis was made. Following a period of treatment with digitalis and Lugol's iodine, a subtotal thyroidectomy was carried out by Mr. Hugh Donovan in October. She made a satisfactory convalescence and was discharged home on the twelfth day after operation.

Histological report on the gland was as follows: " The gland is divided up by broad dense bands of fibrous tissue into lobules. The epithelium in these areas stains well and is slightly more prominent than usual. Colloid, however, is plentiful and only here and there exhibits a foamy appearance. The histological picture suggests that the thyroid hyperactivity is not a very marked feature."

At home she carried on normally until about one year prior to her final admission when she again became short of breath and unable to do her house duties. She became increasingly dull and disinterested, culminating in a refusal to speak. She was admitted to hospital for the second time in March, 1942. She was then uncooperative, incontinent, and in marked congestive failure (B.P. 105/80). She made no response to therapy. On account of her mental condition she was transferred to a mental hospital, where she died in congestive failure in May.

Post-mortem examination. This was carried out by Dr. Cox twelve hours after death. The body was well-nourished, with very large hands and feet and with marked ascites.

Very thick skull. Brain (1644 g.), normal externally except for small adhesions at tips of frontal and temporal lobes. Pituitary fossa very enlarged. Antra, chronic infected membranes. Frontal sinuses clear. Sphenoids, heavily infected. Teeth, septic and carious.

Lungs, normal in appearance and texture. Sero-sanguinous fluid in both pleural cavities.

Pericardial sac contained 1600 c.c. of straw-coloured fluid. Numerous pericardial adhesions.

Heart covered with thick white fibrinous membrane, the result of old pericarditis.

Heart: weight 900 g. Left ventricular chamber small with greatly hypertrophied walls, maximum thickness 30 mm. (Fig. 5). Right ventricle also hypertrophied but dilated, maximum thickness 8 mm. Left auricle dilated with some increase in the thickness of its wall. Right auricle also hypertrophied and dilated. In the posterior half of the interauricular septum, there was failure of development of the septum secundum, causing a septal defect 22 mm. in diameter. Chordæ tendineæ of mitral valve hypertrophied. The valve cusps themselves were normal as were those of the tricuspid, aortic, and pulmonary valves.

Pulmonary artery, enlarged. At the pulmonary valves, the circumference was 11 cm. Left pulmonary artery, 1 cm. after bifurcation, measured 9 cm. in circumference.

Aorta, hypoplastic, the circumference at the aortic valves being 8 cm.; at the level of insertion of the fibrous remnant of the ductus arteriosus, 6 cm.; and at a point 12 cm. distal to that, 5 cm. There was no atheroma. The pulmonary veins opened into the left auricle while the superior and inferior vena cava emptied into the right auricle.

Free fluid present in the abdomen. Liver (1990 g.) dark and congested. Spleen (164 g.) unusually firm. Kidneys: right (294 g.) normal; left (420 g.) large number of cysts at the upper pole, otherwise normal. Ovaries, large and fibrotic. Uterus, irregular with fibroids on the posterior surface.

Histology. Sections from the kidneys, liver, and adrenals were normal except for congestion. The heart muscle showed no evidence of inflammation. The individual fibres were large with normal nuclei. The pericardium was thickened with many layers of fibrous tissue, but no area of active inflammation could be detected. The pituitary showed poorly staining cells only. There was no adenoma or obvious increase of eosinophilic cells.

Comment. Enlargement of the heart is frequently noted in interauricular septal defect. For example, Roesler (1934) reported the case of a girl, aged 14, with a heart weighing 800 g., while Bedford, Papp, and Parkinson (1941) included in their series of 52 cases the case of a woman, aged 36, with a heart weighing 930 g., although this was associated with rheumatic heart disease and mitral stenosis. The enlargement and hypertrophy in such cases involves the right side of the heart, the left auricle and ventricle appearing sometimes almost as appendages. Commonly the pulmonary artery is much enlarged while the aorta is smaller than normal. In this case there was marked enlargement of the pulmonary artery and the aorta was small: the ratio between the two circumferences was essentially that given by Roesler, 3:2. The cardiac hypertrophy, however, did not involve the right side, throwing doubt upon the role of the septal defect in the production of such massive enlargement. This finding also suggests that the frequent association of septal defect with a small aorta is not always due to the diminished output of the left ventricle as was suggested by Bedford, Papp, and Parkinson.

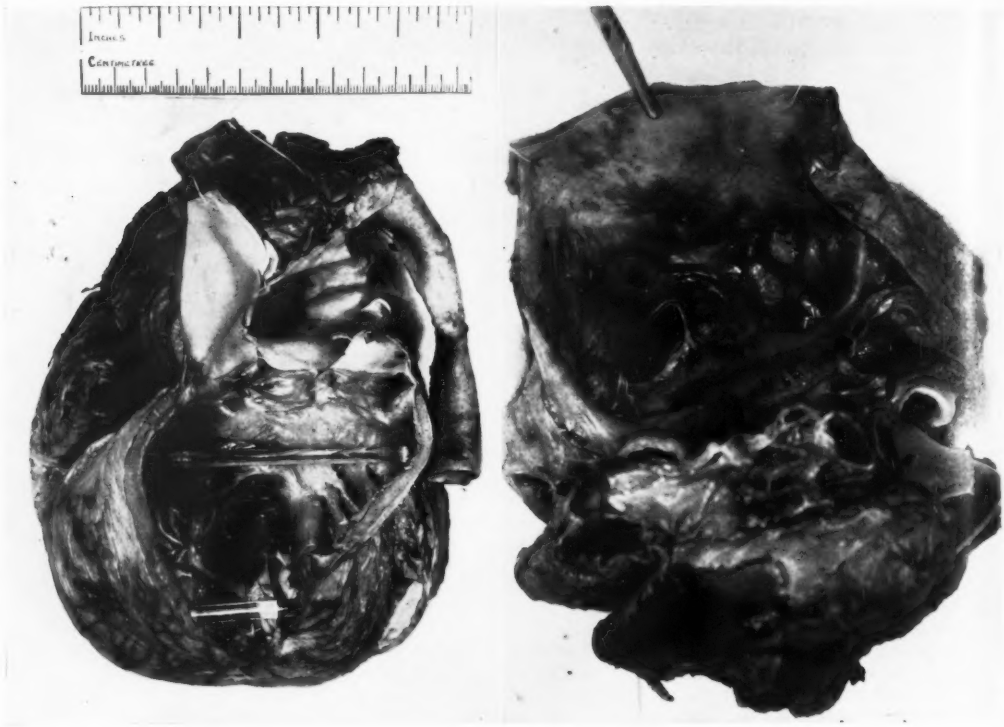


FIG. 5.—Photograph of the heart.

(A) The right ventricle is opened, showing some hypertrophy of its wall, the large pulmonary artery, and the comparatively small aorta.
(B) The dilated and hypertrophied left auricle is opened showing the interauricular septal defect.

Adhesive pericarditis has been noted in atrial septal defects by many writers, *e.g.* by Cossio and Arana (1937), and by Bedford, Papp, and Parkinson (1941), though usually in association with rheumatic valvular disease. The exact ætiology in this case is obscure though it was probably rheumatic. Auricular fibrillation is also common, occurring in 28 cases out of the 62 collected by Roesler; though Bedford, Papp, and Parkinson did not find any recorded case occurring below the age of fifty except in association with mitral stenosis. Finally, there was no evidence in this case that hypertension had been present to account for the enlargement of the left ventricle.

DISCUSSION

Enlargement of the heart usually takes place for two reasons only, either in response to increased work (*e.g.* high blood pressure, valvular disease, or arteriovenous aneurysm) or to the impairment of the heart's metabolism and reserve by rheumatic fever, the anoxæmia of coronary disease, or lack of thyroid hormone or vitamin B_1, etc. In Case 1, none of these intrinsic factors appeared to play any part. It is difficult to assess the role of diabetes with recurrent hypoglycæmia with subsequent impairment of function. It is not probable, however, that this factor caused such hypertrophy in the short space of two years, from the time of onset of his diabetes in 1936 to the time of the first X-ray in 1938. In Case 2, the role of the septal defect was probably small, seeing that the predominant hypertrophy affected the left ventricle whilst there was no evidence of the presence of coronary disease, or of vitamin or thyroid deficiency.

Both large and small hearts may be found in aortic hypoplasia, while hypertrophy, usually attributed to the associated high blood pressure, is frequently found in coarctation of the aorta. This last condition occurs in varying degrees, from constriction that is scarcely recognizable to actual atresia, and may be associated with hypoplasia of the distal aorta, again of varying degrees. In Case 1, there did not appear to be any definite coarctation but there was a rapid diminution in the width of the aorta, commencing just proximal to the fibrous remnant of the ductus arteriosus. In Case 2, the aorta appeared to diminish gradually in size from the aortic valves themselves.

The role played by the narrowed aorta in the production of hypertrophy is obscure and there is very little to be gathered from other reports. The first description of aortic hypoplasia was that given by Morgagni in 1788. King (1841) drew attention to the condition in this country. On the continent, Virchow (1872), Spitzer (1897), Burke (1901), and Apelt (1905), all described cases associated with cardiac hypertrophy but none of them had any data on the blood pressure. Spitzer held that hypertrophy was found if the patient attained adult life; otherwise the heart would be smaller than normal. Virchow attributed the hypertrophy to the narrow aorta and increased elasticity of the vessels. In a number of these early cases changes were noted in the kidneys so that it is probable that high blood pressure was present in some. However, as Apelt pointed out, there was no constant feature in any case by which one could say hypertrophy would be present or not. More recently, Whittle (1929) reported the case of a young man, aged 20, who collapsed and died in the street; other than a recent attack of influenza, there was no record of any previous illness. The autopsy revealed a heart weighing 793 g., with a general enlargement chiefly affecting the left ventricle; the descending aorta was hypoplastic, but it was not specifically stated whether the thoracic aorta was of normal calibre; the remaining organs were normal though the heart was not tested for glycogen. Cluver and Jokl (1942) reported the case of an international Rugby football player who suddenly dropped dead. The arch of the aorta were of normal size but the abdominal aorta measured only half an inch, half the normal size; the heart weighed 482 g.; and the left kidney was the seat of advanced hydronephrosis and pyelo-nephritis. They called attention to the large thymus (26 g.) and the possible secondary effects upon the adrenal and pituitary glands.

It is difficult in the two cases here reported to explain the association of gross hypertrophy and normal blood pressure by any of the accepted physiological concepts. Eyster (1927 may provide some clue as to how such hypertrophy takes place. He showed that, by placing a constricting band around the aorta of dogs for a short period, hypertrophy followed some months later, and he suggested that the temporary dilatation provided the stimulus for the subsequent enlargement. This concept might be extended to these cases. The temporary dilatation to cope with the extra output requirements in strenuous work, might act as the stimulus for the hypertrophy and the finding of a normal blood pressure at rest.

While aortic hypoplasia may have played a large part, we find it difficult to believe that this factor alone would account for such massive enlargement. In Case 1, the heart was almost twice the weight of any of the other recorded cases. Case 2, however, was acromegalic and, in view of other recorded examples, *e.g.* Cushing and Davidoff (1927), and the general splanchnomegaly that occurs, it may be assumed that pituitary dysfunction played a large part in the production of the cardiac hypertrophy. Amsler (1912) attributed such hypertrophy to a direct hormonal action on the heart, while Courville and Mason have reported two cases suggesting that enlargement of the heart may precede the development of obvious signs of acromegaly. They stressed the high incidence of hypertrophy and heart failure and the infrequency of high blood pressure in acromegalics, and concluded that the hormonal theory offered the most satisfactory explanation for the cardiac enlargement.

In Case 1, the very variable response of the diabetes and the symptoms suggestive of thyrotoxicosis were clinical features that pointed to a primary pituitary defect. Therefore, if only

for the sake of directing future observations to the possibility in obscure cardiac hypertrophy we would suggest that excessive action of the anterior lobe of the pituitary gland may have played a part in producing the extreme enlargement found in this patient. Unfortunately, owing to an oversight, no sections were made of the pituitary gland.

Finally, we can only agree with Sir Thomas Lewis (1933) that "There is still much that remains to be explained: it is clear that there must be hidden sources of increased work or the conclusion that increased work is the cause of hypertrophy needs revision."

Summary

Two cases of extreme cardiac hypertrophy are reported.

In the first, a male diabetic, aged 33 years, the heart weighed 1350 grams. There was no associated valvular disease and only moderate increase in the size of the heart chambers. The descending part of the thoracic and abdominal aorta showed moderate hypoplasia. No definite cause for this extreme cardiac hypertrophy could be found, but there was evidence of thyrotexicosis and it is suggested that pituitary hyperfunction played some part.

In the second, a female acromegalic, aged 35 years, the heart weighed 900 grams. The hypertrophy affected the left ventricle predominantly and was associated with an interauricular septal defect and hypoplasia of the aorta. The pituitary dysfunction was thought to have played the chief part in the production of the enlargement in this case.

We are indebted to Professor Haswell Wilson for the pathological report of Case 1, and we wish to thank Dr. Oscar Brenner for the clinical details, Dr. Pickworth and Dr. Cox for pathological and microscopical reports in Case 2, and Dr. T. C. Graves, Medical Superintendant, Rubery Hill Hospital, for facilities granted.

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EISENMENGER'S COMPLEX

BY

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An opening at the base of the interventricular system in association with other defects is one of the commonest of congenital cardiac lesions. The usual combination is Fallot's tetralogy, which consists of a ventricular septal defect, dextraposition of the aorta, and stenosis of the pulmonary artery, with cyanosis.

A much rarer condition is that known as the Eisenmenger complex, where dilatation of the pulmonary artery occurs instead of stenosis, together with dextra-aorta and septal defect. This condition was originally reported by Dalrymple in 1847. Eisenmenger (1897) presented the first complete study of such a case, in which the diagnosis had been made during life by his colleague, von Schrotter.

In 1927, Maud Abbott described 8 cases, 3 of which she had studied personally. According to Baumgartner and Abbott (1929) the condition can be differentiated clinically from Fallot's tetralogy by the following points :—

(1) absence of, or only a moderate degree of clubbing and cyanosis,
(2) the localization over the præcordium of a harsh systolic murmur at the defect, not transmitted into the vessels of the neck,
(3) the occasional presence of a diastolic murmur of pulmonary insufficiency, and
(4) the distinctive character of the X-ray picture.

Hoarseness and aphonia, from pressure of the huge pulmonary conus on the recurrent laryngeal nerve, sometimes occur. Pulsation of the dilated pulmonary artery may be felt, and abnormal dullness percussed at the left base. The midsternal systolic murmur of the Eisenmenger complex is transmitted downwards to the right and to the left, as well as through to the back, whereas in the Fallot tetralogy it is usually transmitted upwards into the neck vessels and through to the back.

Polycythæmia, varying from 7,000,000 to 12,000,000 red cells, is a feature of Fallot's tetralogy, but not of the Eisenmenger complex.

Case Report

A male, aged 15, had been a " blue baby " at birth in 1928, and was troubled with his chest in infancy and childhood. He always had a high complexion and frequently had a bleeding nose ; he was breathless on exertion.

There was nothing of interest in the family history.

During the period 1934–1937 he was in hospital three times with an exacerbation of his chronic bronchitis, complaining of præcordial pain on exertion, a hard dry cough, and attacks of respiratory embarrassment at night. A diagnosis of congenital pulmonary stenosis was made, and in 1937 a poor view was taken of his prognosis. Arrangements were made for his reception in a hospital for incurables ; but on arrival there with his mother he created such a disturbance that he had to be taken home : he had always been a noisy and obstreperous patient.

In 1943 the lad, now 15 years old, was seen during the course of a routine follow-up. His general health had been much better since his discharge from hospital, and he now led a very active life, although inclined to be troubled by bronchitis during the winter months. He no longer suffered from epistaxis or from præcordial pain, but sometimes took a stitch in the side when he " hurried up hills."

On examination he was small for his age but powerfully built. There was a tinge of cyanosis in the cheeks and lips, but no clubbing of the fingers. The pulse was regular in time and force, the rate 80, and the wave of good volume and well-sustained. His blood pressure was 110/80.

The left side of the chest was a little more prominent than the right, and there was diffuse pulsation in the fourth, fifth, and sixth interspaces. The apex beat was felt in the sixth space, four and a half inches from the mid-sternal line. It was diffuse and forcible. A thrill was palpable at the base, the point of maximum intensity being in the third left interspace just lateral to the border of the sternum. On percussion both the right and left borders of the heart were greatly enlarged, and the dilated pulmonary artery could also be made out, the dullness in the second left interspace extending two inches from the mid-sternal line.

On auscultation the predominant feature was a systolic murmur. It was best heard at the point of maximum intensity of the thrill but was audible all over the præcordium. It was mainly conducted downwards to the right and to the left, and through to the back, but was not heard in the neck vessels. The pulmonary second sound was inaudible beneath the prolonged systolic murmur in this area, but a distinct diastolic murmur could not be distinguished. In the aortic and mitral areas the second sound was pure and closed.

No evidence of recurrent laryngeal involvement could be found. There was an undescended testicle on the right side. Blood examinations had been carried out on various occasions, the red count varying from 5·2 to 5·5 million, and the hæmoglobin from 108 to 116 per cent. The Wassermann reaction was negative.

The chief features on X-ray examination were (*a*) great enlargement of the right ventricle, (*b*) no demonstrable enlargement of the left auricle, (*c*) a right-sided aortic arch, displacing the œsophagus forward, and (*d*) prominence of the pulmonary artery (Fig. 1 and 2).

The chief features of an electrocardiogram in 1934 were a normal sinus rhythm with runs of complete dissociation, and right axis deviation (Fig. 3). A record in 1941 showed disappearance of complete dissociation. There was an increase in the height of the P waves in

FIG. 1.—Radiogram showing hypertrophied right ventricle, dilated pulmonary artery, and dextra-aorta.

FIG. 2.—Left (II) oblique position, showing forward displacement of the œsophagus by the right-sided aortic arch.

leads I and II. The QRS interval had increased from 0·06 to 0·12 sec. Inverted T waves had developed in leads II and III, and an S–T depression in lead II. The sternal lead showed depression of S–T, and a diphasic T, while there was a steep inversion of the T wave in

FIG. 3.—Cardiogram taken in 1934, showing right axis deviation and runs of complete dissociation.

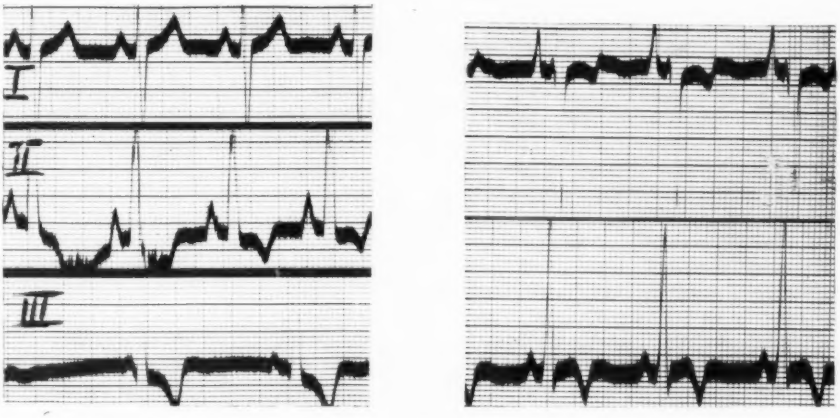

FIG. 4.—Cardiogram taken in 1943, showing larger P waves, especially in lead II, and (usually) normal rhythm. On the right : sternal C_2F above, and apical C_4F below.

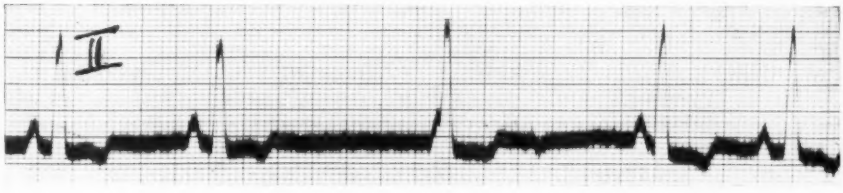

FIG. 5.—Cardiogram taken in 1943, showing occasional dissociation.

the apical lead. In 1943, little further change was recorded (Fig. 4). Infrequent runs of complete dissociation could be made out (Fig. 5), but normal sinus rhythm predominated.

Aetiology

According to the theory of Spitzer (1923) so enthusiastically endorsed by Maud Abbott in her monograph, the critical period of heart formation lies between the fifth and eighth weeks of embryonic life, i.e. before the cardiac septa are formed. During this time, the complex processes of torsion, involution, re-adjustment, and fusion, necessitated by the development of the heart from a simple tube to a four-chambered structure, are taking place. The appearance of the heart in the tetralogy of Fallot is highly suggestive of the relationships that would result from the uncovering of the right reptilian aorta and the obliteration of the left, in the delayed torsion of Spitzer's theory.

The dilatation of the pulmonary artery in the Eisenmenger complex has been attributed to inflammatory lesions. Thus in Blechman and Paulin's case (1922) a streptococcal endarteritis was thought to be the cause of the dilatation. In Stewart and Crawford's case (1933) the histology of the pulmonary arteries suggested an inflammatory process. The authors gave reasons for ascribing the inflammation to a syphilitic infection, but their evidence was based purely on the histological appearances. In their case they found also an old healed endocarditis of the pulmonary valve, and in addition atherosclerotic changes in the pulmonary arteries. They suggest that the syphilitic infection might have been congenital and the chief cause of the cardiac anomalies, and that the pulmonary dilatation was quite possibly due to the arteritis.

Taussig and Semans (1940) describe a case of Eisenmenger's complex in a negro, aged 7 ; a healed lesion of the aortic valve was present, the extensive fibrosis and hyalinization showing it to be of long standing : they question whether the lesion was the result of healed bacterial endocarditis, or really related to the congenital malformation.

Inflammatory changes are frequently found in association with abnormal blood streams in the heart. Thus in *Maladie de Roger* sub-acute endocarditis commonly occurs around the margins of the septal defect and upon the wall of the right ventricle opposite the defect (Abbott, 1936). Moschcowitz (1914) described active non-rheumatic vegetations in congenital heart disease, and according to Boldero and Bedford (1924), the determining factor seems to be the access of arterial blood to the right side of the heart.

The balance of evidence is in favour of the view that the inflammatory lesions in the right circulation arise primarily as a result of the congenital abnormality. That they were so marked and widespread in Stewart and Crawford's case is no doubt related to the advanced age to which this patient lived (60 years).

The pulmonary dilatation and atherosclerosis are more simply explained as a sequel of the increased pressure in the right heart. Certainly in cases of septal defect only, very great dilatation of the pulmonary arteries may occur, with subsequent pulmonary fibrosis and the production of Ayerza's disease. Such dilatation cannot take place in Fallot's tetralogy, owing to the deformity and constriction of the lower pulmonary bulbar orifice.

Prognosis

The prognosis in these cases is the only point of practical clinical interest. The pulmonary stenosis of the Fallot type forces a good proportion of the venous blood to enter the overriding aorta. This causes the cyanosis, the polycythæmia, and the very marked clubbing. The combination of defects is obviously a very serious one, and the average life is 12 $^{3}/_{4}$ years, although Paul White's case (1929) attained 59 years.

In the Eisenmenger type of anomaly, the dilatation of the pulmonary artery does not hinder the entrance of venous blood into the lungs. The shunt normally takes place from left to right and little mixture of venous and arterial blood occurs. Clubbing and cyanosis are therefore slight or absent, and polycythæmia is not a feature.

The prognosis is rather better than in the Fallot type, and the average life is 16 years.

Stewart and Crawford's case (*loc. cit.*), in spite of hard living, reached 60 years, untroubled by his cardiac abnormality.

The lad described in this paper presents all the clinical features of the Eisenmenger complex, and the X-ray examination supports the diagnosis. Although he had a stormy childhood, much troubled by bronchitis, in recent years his health has been much better. At his present age of 15 he leads a very active existence, and refuses to consider any curtailment of it. Rising at six every morning, he does a paper round before going to school. In his spare time he takes his full share in the activities of his group of boy scouts, joining in their physical training, their rough games, and their week-end hikes.

Summary

A case presenting the clinical and radiographic features of the Eisenmenger complex is described, and the ætiology and prognosis briefly discussed.

I have to thank Professor D. M. Lyon for his help and advice.

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CASUAL AND BASAL BLOOD PRESSURES
I.—IN BRITISH AND EGYPTIAN MEN

BY

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In the course of clinical investigations on healthy Egyptian men, we observed that during a period of rest in the sitting posture the systolic blood pressure often fell below 90 and usually below 100 mm. of mercury. This led to a study of the blood pressures of British subjects resident in Egypt and of others resident in London. The pressure found under the conditions described below is called basal* blood pressure because it was not found possible to reduce it appreciably below this level by rest or sleep. Our observations in a physiological type of low blood pressure may be of interest in relation to low blood pressure which is thought to be pathological.

METHOD

Measurements of the blood pressure were made by the auscultatory method, either with manometers in which the whole of the mercury column was visible, or with those of the Baumanometer type which had been checked by an ordinary mercury manometer. The diastolic pressure was taken at the moment when the arterial sound becomes muffled, usually 5 mm. higher than that at which the sound disappeared. The blood pressure was measured on the left arm with the subject sitting in a quiet, warm room. All subjects were instructed to find a comfortable posture, and then to remain still and with the mind blank throughout the half-hour or longer period during which the measurements were made. No conversation was allowed. The observer avoided unnecessary movement, and as a rule no third person entered the room during this time. To allay apprehension the subjects were informed that the investigation would be confined to the repeated measurement of blood pressure. Most subjects became somnolent but in general did not sleep.

The blood pressure was measured as frequently as possible during the first three minutes after adopting the sitting posture. Blood pressure readings were then taken every few minutes throughout the half-hour period of rest, in order to habituate the subject to the procedure of blood pressure measurement. Without habituation of the subject by the continuous presence of the observer and by repeated measurements, the blood pressure falls are less than those we report. Towards the end of the half-hour period the measurements of the blood pressure were made at intervals of about one minute.

RESULTS

In Fig. 1 are recorded systolic blood pressures and in Fig. 2 diastolic pressures. The height of a patient's blood pressure, under the stated conditions, is indicated by the distance of the cross from the left-hand side. For each subject three systolic and three diastolic pressures are recorded in the diagrams, namely:

* The term "basal blood pressure" has already been used in the Joint Report of the Committees appointed by the Cardiac Society of Great Britain and Ireland and the American Heart Association, on the Standardization of Methods of Measuring the Arterial Blood Pressure. "In detailed researches on blood pressure the use of a basal pressure might be considered after preparation similar to that used for basal metabolism. It should be determined 10–12 hours after the last meal of the previous night, and after resting half an hour in warmed room."—EDITOR.

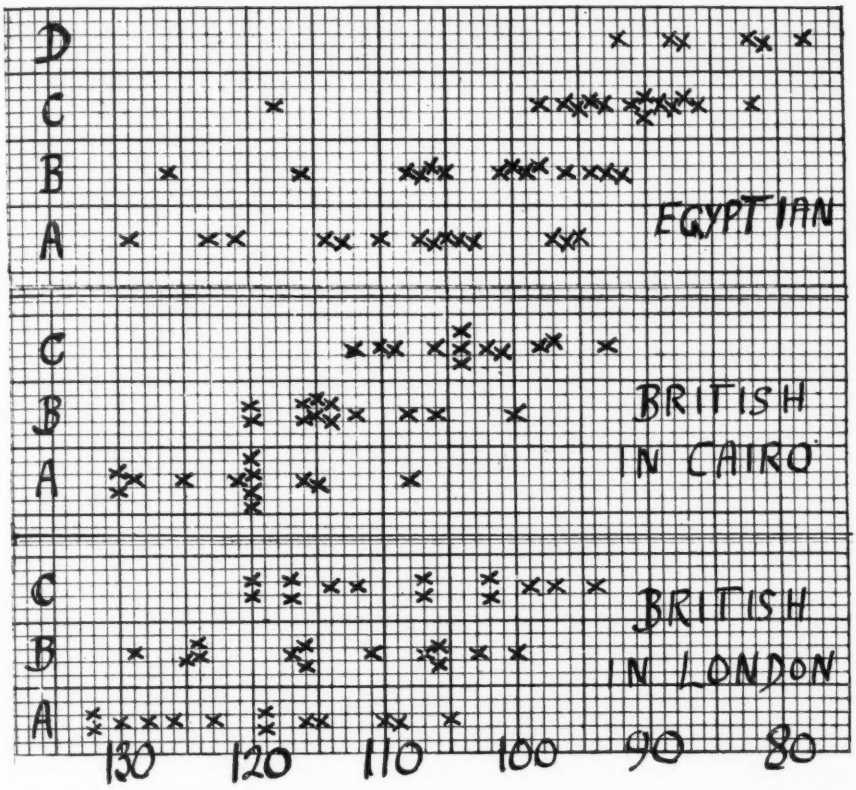

FIG. 1.—Effect of rest and emotional desensitization on the systolic blood pressure in 14 Egyptian nationals (above), in 12 British in Cairo (middle), and in 13 British in London (below). (A) Casual blood pressure. (B) Lowest pressure of the same subjects during the next 3 minutes. (C) Lowest level maintained for three consecutive readings during 30 minutes. (D) Level attained after 90 minutes. Details of the procedure followed during this period are set out under "Method."

(A) The casual blood pressure, which was measured soon after the patient entered the room and was seated;

(B) The lowest pressure measured in the next three minutes; and

(C) The basal blood pressure, which was the lowest level of the blood pressure that was maintained for three consecutive readings during the half-hour period of rest and habituation of the subject to the presence of the observer and to the procedure of blood pressure measurement.

The average levels of the systolic and diastolic pressure do not differ appreciably in the two British groups, but there is an evident difference between these and the Egyptian group. Casual blood pressures are lower and basal pressures are much lower in Egyptian nationals, approximately half the basal systolic pressures lying between 80 and 90 mm., and half the diastolic pressures between 50 and 57 mm. (Fig. 1 and 2).

The blood pressure measurements on British nationals in London were made during a hot, moist August. The pressures of British residents in Egypt and of the Egyptians were measured in Cairo, mostly in April and May, with a higher temperature and lower humidity than London in August. The Egyptian subjects referred to above were of the poorer classes, but the low pressures encountered were not due to malnutrition, since equally low pressures were observed also in well-nourished Egyptian students and doctors of a similar age group. These observations are supported by a considerable number of blood pressure readings made

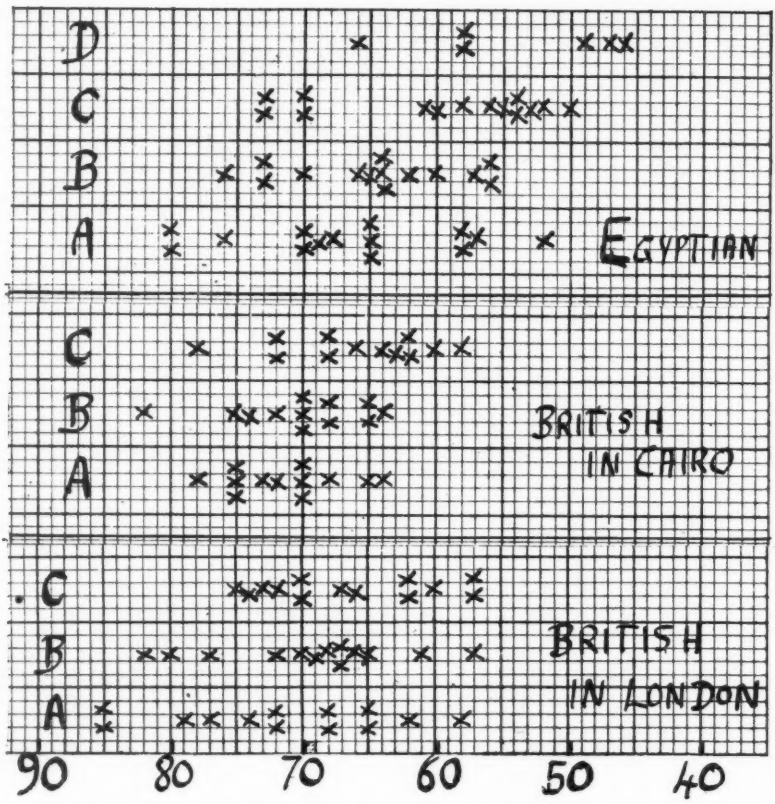

FIG. 2.—Effect of rest and emotional desentitization on the diastolic blood pressure in British and Egyptian nationals. (A), (B), (C), and (D) as in Fig. 1.

in the course of clinical investigations on patients without disease of the cardiovascular system. There seems no doubt that, under comparable conditions, both richer and poorer classes of Egyptians, whether heavy meat eaters or vegetarians, have lower blood pressures, especially basal pressures, than the British, and this difference is not explained to any great degree by the character of the food or by other differences in the environment. Arterial hypertension is, nevertheless, a frequent condition among in-patients in Egyptian hospitals.

The average of the casual blood pressures and of the basal blood pressures in young British and Egyptian nationals are set out in Table 1.

TABLE 1

	Number studied	Average Blood Pressures	
		Casual	Basal
British	25	121/71	106/67
Egyptian	14	110/66	91/59

DISCUSSION

It is well recognized that the blood pressure is variable and is raised by emotion. In the many statistical studies concerned with the level of the blood pressure in health the figure recorded is for the casual blood pressure, in that usually few precautions are taken to guard against the pressor effects of emotion.

The normal European systolic pressure during sleep is of the order of 95 mm. of mercury (Müller, 1921; Brooks and Carroll, 1912). Some of the above observations were made during natural sleep, and in others sleep was induced by hypnotics such as sodium barbitone. In British subjects, the average basal systolic blood pressure with the subjects awake is about 106, which is 5 to 10 mm. higher than the reported average levels of the systolic pressure attained after some hours of sleep. If the patients fell asleep during the investigation no appreciable difference between the waking and sleeping pressures was noted. The possibility that the blood pressure falls further if sleep continues has not been studied. In a few Egyptians the measurements of blood pressure was continued for a period of three hours and further falls of blood pressure occurred; in five out of six the systolic blood pressure fell below 90 and in one to 78; in no case did any symptom develop.

The observer and his sphygmomanometer represent a stimulus that raises the blood pressure, and emotional habituation to both is required before a low level of the pressure is obtained. There is a widespread recognition of the variability of the blood pressure in health, and it is commonly stated that the figure which should be recorded is the lowest attained under conditions of rest. The pressures usually recorded under conditions of rest lie, with few exceptions, within the range of what is commonly regarded as normal. A considerable proportion, however, of our measurements made in healthy subjects at rest but with deliberate emotional desensitization, fall to levels commonly thought to be pathological (below 110–100, according to various authors).

In general, basal blood pressures cannot be obtained by repeated measurements made in a hospital ward, with or without screens about the bed; nor in subjects who suspect that the blood pressure measurements are only a prelude to further procedures. The environment of the subject must be entirely unstimulating. Restlessness on the part of the observer, noises outside the room, and displays of medical equipment may invalidate the result. In other words, observations on man require experimental conditions similar to those which Pavlov (1927) found essential in his conditioned reflex experiments on dogs. Emotional desensitization of the human subject by continued repetition of the stimulus and avoidance of new and especially of unfamiliar stimuli, bears a close resemblance to some of the experiments of the Pavlov school on conditioned inhibition in the dog.

Sometimes the blood pressure fell to a level which, encountered in surgical shock would indicate a dangerous condition. Under physiological conditions such low blood pressure is rarely observed with casual measurements. The difference between the casual and basal blood pressures varies considerably with different subjects. It may well be that many patients considered to be examples of hypotension have a normal basal blood pressure, but sub-average degrees of elevation of the casual above the basal pressure.

Summary

Egyptian men resident in Egypt have much lower blood pressures than British men resident either in Egypt or in England. This difference does not depend upon differences of temperature, diet, or social status.

Half an hour of rest in the sitting posture, together with deliberate emotional desensitization to the presence of the medical examiner and to the procedure of blood pressure measurement reduced the systolic blood pressure to below 100 in 13, and to below 90 in 5 out of 14 Egyptian men ; and to below 105 in 13, and to below 100 in 6 out of 25 British men.

Such lowering of the blood pressure was not associated with any symptoms.

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CASUAL AND BASAL BLOOD PRESSURES
II.—IN ESSENTIAL HYPERTENSION

BY

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Received June 1, 1943

The casual and basal blood pressures were determined in 27 Egyptian patients with essential hypertension, using the method described in the previous paper. Consideration has been given to the practical value of such measurements and to their bearing on the functional pathology of essential hypertension.

Results and Discussion

In half-hour periods of observation it was noted that physical and mental rest and habituation to the presence of the observer and his sphygmomanometer led to falls of blood pressure in essential hypertension greater than those which occur in health (Fig. 1 and 2). Thus in half-hour periods the average fall of systolic pressure in 14 healthy Egyptian subjects was 15 mm. of mercury, but in 13 Egyptian patients with essential hypertension (average systolic blood pressure about 200 mm.) the average fall of systolic pressure was 36 mm. The diastolic blood pressure in essential hypertension also exhibited a fall which was greater than that encountered in healthy subjects, being 18·5, as against 6·5 mm. in health.

In both hypertensive and healthy subjects further decreases in pressure could be obtained

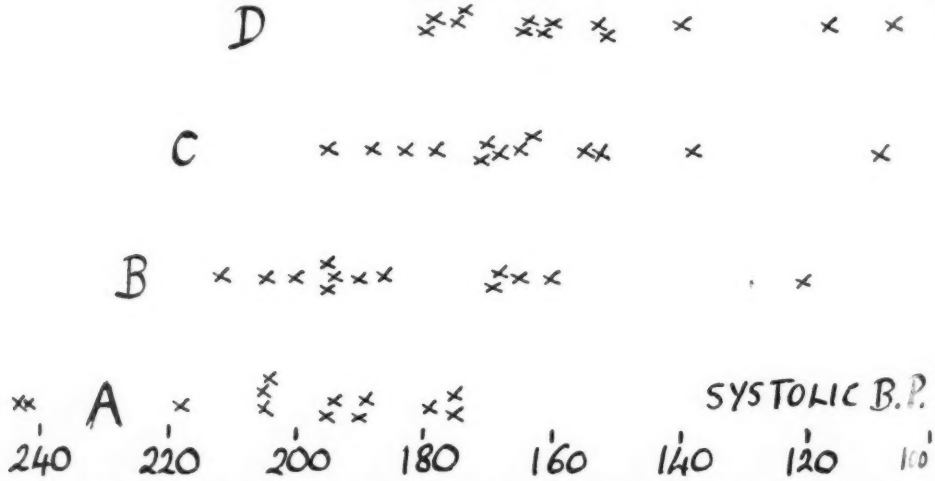

FIG. 1.—Effect of rest and emotional desensitization on the systolic blood pressure in essential hypertension (Egyptian nationals). (A) Casual blood pressures of 13 subjects with essential hypertension. (B) Lowest pressures of the same subjects during the next three minutes. (C) Lowest level maintained for three consecutive readings during half an hour. (D) Level attained after 2–4 hours. Details of the procedure followed during this period are set out under "Method."

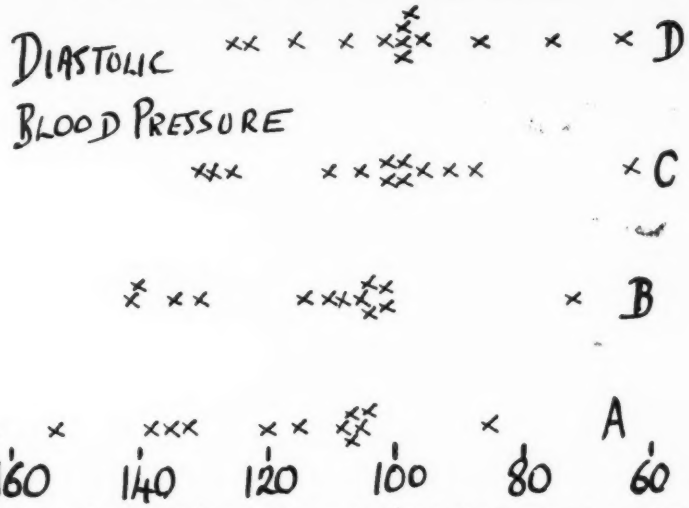

FIG. 2.—Effect of rest and emotional desentitization on the diastolic blood pressure in essential hypertension (Egyptian nationals). (A), (B), (C), and (D) as in Fig. 1.

by extending the period of rest to between 2 and 4 hours. In 27 patients with essential hypertension (including the 13 mentioned above) the average casual systolic pressure was 195 and the average pressure after 2–4 hours rest and habituation to the process of blood pressure measurement was 151. The average casual diastolic pressure was 116 and the average basal diastolic pressure 95. The systolic pressure fell to 77 per cent of its initial level and the diastolic pressure to 82 per cent. It would appear that in essential hypertension a period of about two hours rest and habituation to the process of blood pressure measurement is required before basal readings of the blood pressure are obtained.

In the course of our measurements patients occasionally fell asleep. In sleep of short duration the blood pressure did not fall appreciably below the basal level recorded with the subject awake. This observation and comparison of our basal blood pressure readings with those recorded during sleep by various authors (Brooks and Carroll, 1912; Müller, 1921), suggest that we are probably justified in describing the measurements we have made as basal pressures, since the blood pressure taken with the patient awake does not differ greatly from the blood pressure during the first few minutes of sleep.

The basal blood pressure cannot be guessed from knowledge of the casual blood pressure. In two patients each with casual systolic blood pressures of 195 mm. the basal blood pressures after two hours were 160 and 130 mm. One exceptional patient (European) had a casual systolic pressure of 290 with a basal systolic pressure of 130. It seems probable that the basal blood pressure is a fair indication of the resistance to contractions of the left ventricle during the hours of sleep, and that, in general, the work of the heart will be less for the lower basal pressure. The basal blood pressure may, therefore, be of assistance in determining prognosis.

It is common knowledge that in patients with essential hypertension the blood pressure usually falls appreciably during the stay in hospital. Physical rest in hospital is accompanied by familiarity with and emotional desensitization to procedures such as blood pressure measurement. Nevertheless, the lowest readings of the systolic pressure recorded casually in the wards are much higher than the blood pressure which may be attained in half an hour by the method we have used.

Much of the difference between casual and basal blood pressure is of mental origin, as is indicated by the following observations. In four patients with essential hypertension the

blood pressure was reduced to its basal value by rest and habitation to the presence of an observer, called observer 1, using the method described in the previous paper. Observer 2 then entered the room, conversed with the patient, and measured the blood pressure. The visit of observer 2 corresponds to an ordinary contact between doctor and patient; although a basal level of the blood pressure had been secured by observer 1, the pressure did not remain basal in the presence of observer 2. The blood pressure readings obtained by observer 2 were in all cases nearer to the casual than to the basal blood pressure. It was immaterial in this investigation which of the authors played the part of observer 2. Similar observations have been made on healthy subjects but with less striking pressure differences It appears therefore that in health and essential hypertension the difference between the levels of the basal and casual blood pressures depends to an appreciable degree upon the mental processes of the patient. Probably the difference is due to the stimulation of vasomotor nerves, but might be explained by the liberation of a vasoconstrictor substance. If, however, the liberation of a vasoconstrictor substance is responsible for the degree to which the casual blood pressure is higher than the basal blood pressure, then the substance is unlikely to be either adrenaline or posterior pituitary hormone, since amounts of these sufficient to influence the blood pressure appreciably cause striking pallor.

Fishberg (1939) refers to an interesting case of hypertension resulting from an emotional state, described by Mueller (1922), in which elimination of some domestic friction led to a fall in the systolic blood pressure from 280 mm. to 150 and finally to 130 mm. In the course of our investigation we had three experiences that indicated how adverse emotion may make it impossible to obtain a true basal level of the blood pressure. During this investigation, one of our collaborators arranged to administer a general anæsthetic to some of our patients with essential hypertension, partly with a view to determining their suitability for surgical treatment and partly to discover whether the blood pressure during anæsthesia was appreciably lower than that observed under basal conditions. (It was not much lower.) One such patient, when first seen, had a casual pressure of 220 and a basal pressure of 153. On the next day, however, his casual pressure was 264 and the basal pressure was 223. Between the first and second observations this patient had learnt from others in the ward that it was probably our intention to administer an anæsthetic and he had expressed his unwillingness. The man was then informed that no anæsthetic would be given and no more elaborate investigations would be made than those he had experienced already. On the afternoon of the same day, a further study of the casual and basal pressures was made, and it was found that both of these had returned to the original levels. Two other experiences of this kind have been encountered, where fear of anæsthesia made it impossible to obtain a true basal pressure and where the removal of the known cause led to a considerable fall in both the casual and basal pressure. It would appear not unlikely that some of the blood pressure decrease following surgical treatment of hypertension is due to a lessening of emotional tone when the operation is over.

A further example of the effect of emotion is seen in the examination of recruits for military service. A consecutive series of 20 men whose blood pressures were found elevated at the routine examination for military service were referred for a second examination. On re-examination under quiet conditions and with the measurements taken repeatedly for about three minutes much lower blood pressures were obtained (Fig. 3). It is of interest that the apex beat was outside the mid-clavicular line in five instances and in two of these the blood pressures at the second examination were below 145 systolic and under 70 diastolic. Evans and Loughlan (1939), in a comprehensive paper on the drug treatment of hyperpiesia, indicate clearly the manner in which blood pressure changes of emotional origin have led in the past to unsatisfactory evaluations of the effects of drugs.

In clinical practice "essential" hypertension refers to elevation of the casual blood pressure. As an average, about half of the elevation above normal of the casual blood pressure, in essential hypertension, represents an increase that depends upon the response of the patient

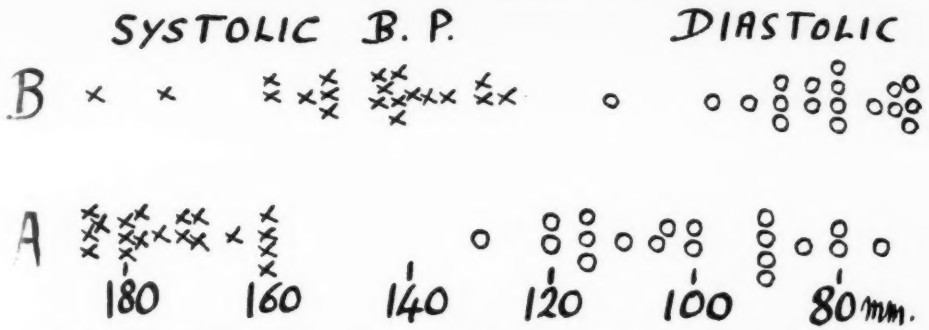

FIG. 3.—Systolic and diastolic blood pressure of recruits with high pressure taken under two different conditions (New Zealand nationals). (A) Systolic and diastolic blood pressures as measured during routine examination of 20 hypertensive recruits. (B) Systolic and diastolic blood pressures of the same men at a re-examination under quiet conditions where 2 or 3 minutes were allowed for the blood pressure to settle.

to mental, emotional, and physical activity in that as an average the blood pressure falls half the way towards normal when the influence of such factors is removed in a relatively short time, by sleep or by a process of physical rest combined with deliberate emotional desensitization. The part played by such factors in determining the degree of elevation of the casual above the basal blood pressure varies in different patients, so that the level of the casual blood pressure does not provide an estimate of the probable basal pressure.

The lability of the blood pressure in a case of essential hypertension may be judged by the degree of difference between the casual and basal pressures. In Fig. 4 it is seen that the patients with the more labile blood pressures are in general those with higher casual blood pressures, but their basal blood pressures are no higher than those of essential hypertension

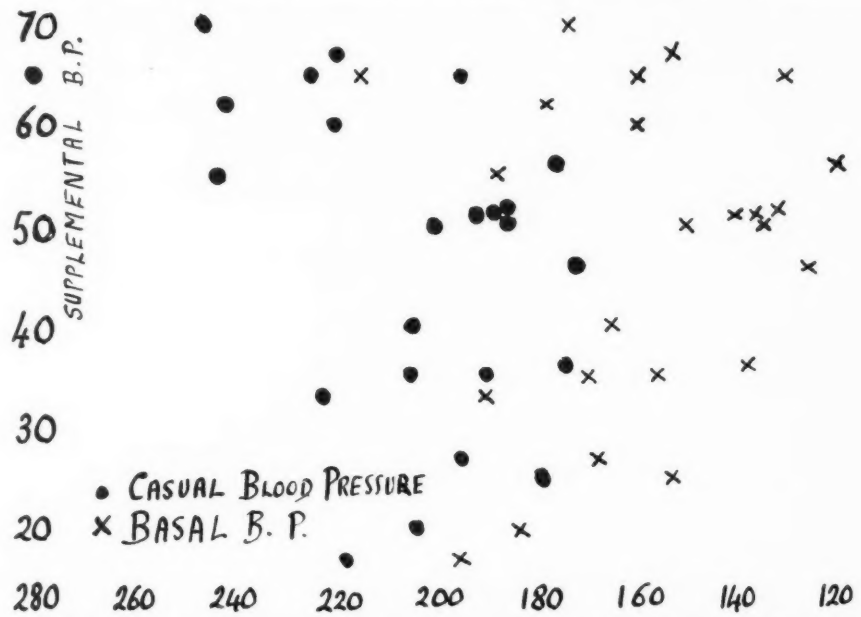

FIG. 4.—Relationship between supplemental (casual minus basal) pressure and the heights of the casual and basal systolic blood pressures. The distribution of points suggests that a rise in the supplemental pressure tends to be associated with a rise in the casual blood pressure but not so much in the basal blood pressure.

patients with less labile pressures.* Thus, if we compare subjects where the differences between the casual and basal blood pressures are between 50 and 70 mm. of mercury with those where the difference lies between 20 and 40, we find that the average of the basal blood pressures does not differ in the two groups whereas the casual pressure is much higher in the 50 to 70 mm. group than in the 10 to 20 mm. group. Hence it would appear that the basal blood pressure is not much influenced by the lability of the blood pressure. It has been shown already (Alam and Smirk, 1938) that the level of the *resting* blood pressure in health shows no correlation with the sensitivity of the subject to blood pressure raising reflexes. Probably the relative importance of the amount of emotional activity and the degree of increased susceptibility to blood pressure raising reflexes, in determining the level of the casual blood pressure, varies from case to case.

It seems desirable to regard the casual blood pressure as made up of two parts, namely, the relatively stable basal blood pressure and a variable " supplemental " pressure. The supplemental pressure is that part of the casual blood pressure which is elevated as the result of the patient's physical, mental, and emotional activity, chiefly the latter, the elevation of the basal blood pressure requires some other explanation.

Summary

In essential hypertension considerable differences exist between the casual blood pressure (i.e. as ordinarily measured) and the basal blood pressure. In a group of 27 patients with essential hypertension, the average casual blood pressure was 195/116 and the average basal pressure was 151/95.

The extent to which the relatively variable casual blood pressure rises above the basal pressure may be termed the supplemental pressure. .

The supplemental pressure is that part of the casual blood pressure that represents the response of the cardiovascular system to physical, mental, and emotional stimuli. With rest and habituation to the presence of the observer and his sphygmomanometer, or with sleep, the supplemental pressure falls to, or nearly to, zero.

In Egyptian patients with essential hypertension, both the basal and supplemental pressures are elevated. As an average one-half of the elevation of the casual blood pressure in these cases of essential hypertension is due to elevation of the supplemental pressure which is of a removable nature and due to the effect upon a susceptible individual of his physical, mental, and emotional environment.

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* The suggestion that the height of the casual blood pressure depends mainly on the supplemental pressure, and that the basal blood pressure remained relatively stable did not appear to me to be borne out by Fig. 4. It seemed rather that as the casual pressure increased both the supplemental and the basal pressures increased in proportion. This seems to be confirmed by analysis of the figures. If all the cases are arranged in five groups according to the height of the casual systolic pressure the results are as follows:

casual	*basal*	*supplemental*	*percentage*
246	183	63	25
220	170	50	23
202	165	37	19
195	150	45	23
179	136	43	24

There is a steady decrease in the basal pressure and somewhat similar decrease in the supplemental pressure, the latter forming a fairly steady percentage of the casual pressure in each of the five groups, the figures being 25, 23, 19, 23, and 24 per cent.—Editor.

CASUAL AND BASAL BLOOD PRESSURES
III.—IN RENAL HYPERTENSION

BY

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Received June 1, 1943

In a previous communication it was shown by Alam and Smirk (1938) that the response of the blood pressure to reflexes that raise the pressure was appreciably smaller in renal hypertension than in essential hypertension and even smaller than in health. It is stated by Müller (1921) that during sleep the blood pressure falls much more in essential hypertension than in health or in renal hypertension. It becomes of interest, therefore, to ascertain the relationship between the casual and basal blood pressures in renal hypertension.

Results and Discussion

Our observations were made on chronic cases with a clear history of glomerulo-nephritis, and with a blood pressure of 160 systolic or more. The majority of the patients were Egyptian,

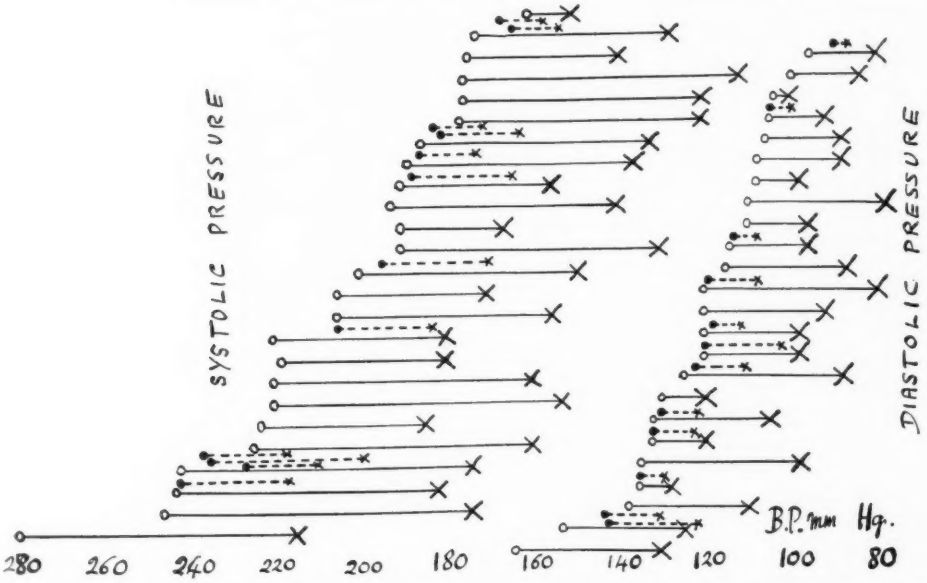

Fig. 1.—Casual and basal blood pressure in renal and essential hypertension. Each horizontal line represents a determination of these pressures, the length of the line indicating the difference between the casual and basal pressure (i.e. the supplemental pressure). The systolic pressures are on the left, the diastolic on the right. Continuous lines represent essential hypertension and dotted lines renal hypertension.

○=casual pressure in an essential hypertension case. ×=basal pressure in an essential hypertension case.
●=casual pressure in a renal hypertension case. ×=basal pressure in a renal hypertension case.

The results are arranged with the higher casual pressures below and the lower above.

and in this the results may be compared with casual and basal pressures obtained in healthy Egyptians or in Egyptians suffering from essential hypertension. A number of additional observations, made on New Zealand patients, are included. The casual and basal blood pressures of hypertensive patients are set out in Fig. 1, and it will be observed that, in general, the difference between these two pressures is much less when the hypertension is of renal origin than when it is of the " essential " type. This statement applies to both systolic and diastolic readings. Hence in renal hypertension the pressure elevation affects the basal pressure more than the supplemental pressure (as defined in the previous paper).

The observation may be related to the common clinical experience that the blood pressure in chronic renal hypertension cases is less likely to show wide variation during a stay in hospital than in patients with essential hypertension. It would appear that rest and emotion due to unfamiliarity with, or excitement produced by, blood pressure measurements have less effect upon the blood pressure in renal hypertension than in essential hypertension. This observation may be correlated with the decreased susceptibility to reflexes that raise blood pressure, which was demonstrated by Alam and Smirk. It would appear that the blood pressure in renal hypertension is no more reactive to vasomotor stimuli than is the normal blood pressure and is less reactive than the blood pressure in essential hypertension.

Summary

The difference between the casual and basal blood pressure is less in renal hypertension than in essential hypertension.

The pressure elevation affects the basal blood pressure more than the supplemental pressure.

It is likely that the blood vessels in renal hypertension are less reactive to vasomotor impulses than they are in essential hypertension.

We are grateful to Professor Soliman Azmy Pacha for his kindness in extending to us the facilities of his post-graduate department.

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LATENT HEART BLOCK

BY

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Received June 12, 1943

I have used the term "Latent Heart Block" to indicate a prolonged P–R interval without any manifest degree of block, such as dropped beats or 2 :1 block.

This paper is a clinical study of a series of such cases, mainly from the point of view of the ætiology and significance of the condition. One might guess that latent heart block would be found in the same cases as, but at an earlier stage than, higher grades of heart block; and that a patient would progress from latent to dropped beats, next to 2 : 1, and finally to complete heart block. But such a regular sequence is not common.

Shortly, one can say that latent heart block is found in any type of heart disease at any age without much tendency to progress, and that there is a complete contrast with the well-recognized ætiology of complete heart block, which is atherosclerosis and high blood pressure in elderly patients. As might perhaps be expected, latent block is more often transient than is the case with complete block, but it is often persistent at a fairly steady level for long periods. It is also seen—sometimes to an unusual degree—in hearts that appear to be normal otherwise; here it may be an extreme instance of vagal activity (Fig. 1).

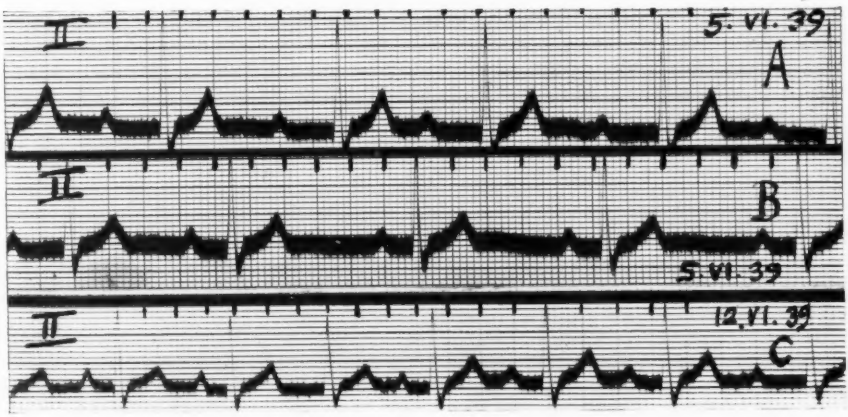

FIG. 1.—An unusual case of latent heart block, with longer and shorter P–R intervals without intermediate grades. From a young man without evidence of organic heart disease. Case 47.
(A) Longer P–R interval of 0·36 sec.
(B) Shorter P–R interval of 0·24 sec., except for the first response.
(C) Shorter P–R interval except for the last response and one instance of ventricular escape.
Of many plates available some showed a long or short P–R interval throughout all three leads, but most showed a change between the leads and some (mainly chosen for illustration) showed a change that was recorded while one lead was being taken.
In this and subsequent plates the time marker indicates fifths of a second, and generally these have been inked in at the top.

This lowest degree of heart block, when there is a prolonged conduction time without dropped beats or any higher degree of block, is, as a rule, only recognizable by graphic methods. Cowan and Ritchie (1922) said that it was not often observed and never caused any symptoms, although the patients in whom it occurred usually had obvious symptoms and signs of heart disease. Lewis (1920) mentioned two signs which might lead to its being suspected—a third sound in diastole owing to the auricular systole being separated from the ordinary ventricular sound, and in cases of mitral stenosis the murmur and thrill being isolated and concentrated at a special moment in diastole. These signs are not common, but the custom of taking more electrocardiograms has shown that the condition itself is common. It has therefore seemed worth investigating, and the term " latent " has been chosen as a convenient one for this variety of heart block. It is a true subdivision of heart block, although as a rule it is only made manifest by instrumental methods. The term incipient, which I suggested originally, seems less suitable because it might suggest that this early stage generally progresses sooner or later to a higher grade of heart block, and this is far from being true of most cases.

Any P–R interval of more than 0·20 sec. has been taken as prolonged, or more strictly one of 0·205 or above, as each has been recorded to the nearest hundredth of a second. Many cases with P–R intervals between 0·19 and 0·20 sec. have a conduction time that is prolonged and pathological for them, but unless cardiograms have been taken before there is no way of distinguishing the normal and abnormal at this level, and it is more practicable and more useful to accept the usual upper limit of 0·20 sec.

Chamberlain and Hay (1939) found the average P–R interval (0·16) 0·17–0·19 sec. in different age groups, but recorded a few normal cases where it was 0·22 sec. Hoskin and Jonescu (1940) in young women found most cases between 0·12–0·18 sec., but a very small proportion between 0·18–0·21 sec., the upper limit of normal originally given by Lewis and Gilder (1912).

The papers just quoted show that a few cases with a P–R of 0·21 or 0·22 sec. are normal, and the present investigation confirms their view; but the omission of all below 0·22 sec. would leave out so many pathological cases.

Paul White *et al.* (1941) have recently emphasized the differences often found in measuring the P–R interval in the different standard leads, that in lead II being generally the longest. This will be admitted by anyone measuring many cardiograms, and it would probably be best to work on a standard taken from lead III, as they suggest. But these cases were seen before realizing the extent of this difference or reading his paper, and generally where there were differences an average figure had been taken. In any case, it would have little effect on the very considerable prolongation found in most of these patients, as only 4 per cent of their series showed a variation up to 0·02 sec.

The present series of cases was obtained by looking through 10,000 consecutive electrocardiograms taken at Guy's Hospital in the twelve years 1927–38 (172 cases) and adding all others (61 cases) I had remembered to index from those seen at the Heart Hospital and in private: the latter would fail to include many with only a slight increase in the conduction time, but few of much interest where it was longer; the former would provide an unselected consecutive series, as when there seemed any doubt the P–R interval was measured.

Ten cases with congenital complete heart block have been omitted as they form a special type that has been reported and discussed elsewhere (Campbell and Suzman, 1934a).

This means that about 2 per cent of all patients sent to a cardiac department show latent heart block and rather more than 1 per cent show some clinical degree of heart block.

The 141 cases with latent heart block only have been divided into three grades; (IV A) 31 cases with a P–R interval of 0·26 sec. and above, (IV B) 45 cases with a P–R interval of

from 0·23 to 0·25 sec., and (IV C) 65 cases with a P–R interval above 0·20 but not more than 0·22 sec.

TABLE I

NUMBER OF PATIENTS WITH LATENT AND HIGHER GRADES OF HEART BLOCK

	Guy's Hospital	Heart hospital and private	Total
Number of electrocardiograms	10,000	—	—
Total number of patients	5,320	—	—
Number with some degree of heart block	172	61	233
I. Complete and/or 2 : 1 block without latent	25	11	36
II. Latent and complete or 2 : 1 heart block	15	12	27
III. Latent heart block and dropped beats	17	12	29
IV. Latent heart block only	115	26*	141
A. P–R, 0·26 sec. and above	*23*	*8*	*31*
B. P–R, 0·23 to 0·25 sec.	*34*	*11*	*45*
C. P–R, 0·20 to 0·22 sec.	*58*	*7*	*65*

* This figure is relatively low because they were not searched for systematically, as were the Guy's cases.

ÆTIOLOGY OF CASES WITH HEART BLOCK

The ætiology of cases with latent heart block is summarized in Table II, and for comparison a series of cases, (I) with complete and/or 2 : 1 heart block *without* latent block, (II) with complete and/or 2 : 1 heart block *and* latent block, and (III) with dropped beats but no higher degree of block, have been analysed and tabulated in the same way. It was found that these three grades and the three grades of latent heart block (IV A, IV B, and IV C) could, as far as ætiology is concerned, be combined into three larger groups.

Those with a P–R interval from 0·20 to 0·22 sec. and those with a P–R from 0·23 to 0·25 sec. were combined because they showed no apparent difference, except that (as might be expected) there were among the former more cases with normal hearts and rather more with thyrotoxic hearts. On the other hand, those with a P–R interval from 0·26 sec. upwards showed a much higher proportion of cases with rheumatic fever and acute infections and a much smaller proportion with thyrotoxic or normal hearts. This was also the case with the patients who showed dropped beats, so these were combined into a second group.

Finally there was little ætiological difference between those with 2 : 1 and/or complete heart block, whether they had or had not also latent block, so these were also combined into a third group.

The figures for these three larger groups are expressed as percentages in Table II, after combining some of the smaller ætiological subdivisions to make comparison as easy as possible. The differences are most striking. In the first group with the least prolonged P–R intervals, up to 0·25 sec., 24 per cent had thyrotoxicosis or no apparent heart disease, both these factors becoming much less significant in the second group and absent in the third group with 2 : 1 or complete heart block. Chronic rheumatic heart disease was also of importance in the first group, being the ætiological factor in 22 per cent; this figure falling to 12 per cent in the second, and to 3 per cent in the third group.

In the second group, with the longer P–R intervals of 0·26 and above or with dropped beats, 41 per cent had active rheumatic fever or other acute infections, while this factor was responsible for only 11 per cent of the first group and for only 2 per cent of the third. No other ætiological factor showed a significantly larger figure in this group than in the first group with a shorter P–R interval.

In the third group with 2 : 1 or complete heart block, there was an even more striking contrast: 69 per cent of the cases, against 29 and 23 per cent in the first and second groups, had myocardial disease as the ætiological factor. Syphilitic heart disease was also much more

prominent in this group, being found in 9 per cent against the insignificant figure of 2 per cent in the two former groups. Primary myocardial disease with syphilitic and hyperpietic heart disease were together responsible for 95 per cent of the cases with 2 : 1 or complete heart block, while in the two former groups these three factors combined were not responsible for more than 43 and 40 per cent. Hyperpietic heart disease alone had a much more regular incidence in the three groups, varying only from 12 to 17 per cent. Further subdivision of the myocardial cases did not reveal any striking differences.

TABLE II

ÆTIOLOGY OF DIFFERENT GRADES OF HEART BLOCK (PERCENTAGES)

	IV B and IV C P–R, 0·20 to 0·25 sec.	IVA and III P–R, above 0·26 or with dropped beats	II and I Complete and 2 : 1 heart block with or without latent block
Tonsillitis and acute rheumatism	11	**41**	2
Chronic rheumatism	**22**	12	3
Syphilitic	2	2	**9**
Hyperpietic	12	15	17
Myocardial	29	23	**69**
Thyrotoxic	**13**	2	0
No apparent disease	**11**	5	0
Total numbers	110	60	63

ÆTIOLOGY OF CASES WITH LATENT HEART BLOCK

There were 110 cases with a P–R interval from 0·20 to 0·25 sec.; few of these call for individual comment except that the presumed normals will be enumerated. Otherwise, the diseases from which they suffered seemed to be much the same as might be expected in any other collection of hospital cases.

Of the 110, 48 belonged to the myocardial group (about equal numbers having raised blood pressure or disease of the coronary arteries or heart failure or a large heart without any of these causes being obvious), 36 to the rheumatic group, 14 to the thyrotoxic group, and 12 to the normal group.

There were 31 cases, where the P–R interval was 0·26 sec. or more. Acute rheumatism or tonsillitis or treatment with digitalis were more often responsible for the longer intervals, and in some cases these were the only cause of the P–R interval being prolonged, but in others there was already some degree of prolongation that was increased by a transient infection or by treatment with digitalis. These greatly prolonged P–R intervals will be considered in more detail later (see p. 175). First, however, certain general points about the ætiological groups will be discussed.

Acute rheumatism. Little need be said about this as the prolonged conduction time of acute rheumatism is well known. Parkinson, Gunson, and Gosse (1920) found some degree of block in 30 per cent of their cases during the acute stage. Cohen and Swift (1924) found it over 0·21 sec. in 22 per cent of their cases and somewhat prolonged in 84 per cent, if any increase of more than 0·02 sec. above the normal for that patient was counted as pathological. In a recent study, Keith (1930) found this small increase in 80 per cent of his cases with clinical evidence of rheumatic carditis; he did not say how many were over 0·20 sec., but as the average figure was up to 0·18, a good many must have been so. He brings forward good evidence that the increase is due to vagal activity and, though his title of "over-stimulation of the vagus nerve" might suggest some central factor which would hardly fit in with the general clinical picture, he suggests that the part involved is the vagal nerve terminations in the heart.

All are agreed about the relative rarity of manifest block in these rheumatic cases: Carey Coombs (1924) had only come across six cases where dropped beats were produced by acute rheumatism.

Examples have already been described (Campbell, 1943) and are pertinent in this connection also, as soon after the dropped beats they had latent block alone. In fact, my own records show few instances of classical rheumatic fever as a cause of latent block only and it was more often recorded after a minor relapse, but this is because cardiograms of patients with rheumatic fever were not taken as a routine at Guy's Hospital, but only when there was some special reason.

The return of the P–R interval to normal may be very quick and complete, even after a severe attack. A boy, aged 18, was admitted with a classical attack and had an irregular heart with dropped beats, generally after P–R intervals of 0·25 and 0·37 sec.; after a week it had fallen to 0·18 sec. (Case 13). Here there was little correspondence between the sedimentation rate and the increase of conduction time, for after six weeks, when the sedimentation rate had only dropped from 98 to 47, the P–R interval was down to 0·16 sec. In a man with a very severe attack, the P–R interval was increased from 0·16 to 0·34 sec. (with some dropped beats that were not graphically recorded); three days later it was 0·25 and a week after this 0·19, and after another week 0·17 sec. (Case 22). In a younger man with an attack of average severity it fell from 0·32 to 0·19 sec. in 18 days (Case 54). These three patients all made good recoveries as regards their heart, and a quick recovery in the conduction time is certainly one favourable sign for a good outlook as regards the heart.

Sometimes the P–R interval is increased considerably from what appear to be very minor relapses. In a young man with mitral and aortic disease, it rose during convalescence from 0·20 to 0·26 sec. with a very minor return of pain and was still 0·24 a month later (Case 31). A girl was convalescent after an attack of chorea and slight carditis, and her sedimentation rate had fallen to 6: her P–R interval increased from 0·21 to 0·28 sec. with no other evidence of a relapse except a rise of heart rate from 80 to 90 (Case 52).

In two severe cases the increase of conduction time was no more than in these minor ones. In a boy of 17 with mitral and aortic disease, where it had been about 0·21 for many years, it rose to 0·28 and, finally, to 0·31 sec. (with associated S–T inversion in leads II and III) in his terminal attack of rheumatic fever (Case 36). In a girl with rheumatic aortic regurgitation, where the P–R interval was generally about 0·21, it did not rise above 0·25 sec. in a recurrent attack with pericarditis that was severe enough to produce fairly deep S–T inversion (Case 85).

It is obvious even from this small number of cases that the increased conduction time is not an accurate measure of the severity of the attack or even of the cardiac involvement. Nevertheless, the quick fall towards or to normal is a favourable sign, and often the changes in heart rate, the sedimentation rate, and the conduction time do seem roughly paralell, so that any one is in that case a good measure of the severity of the attack.

Other acute infections are dealt with later.

Chronic rheumatic heart disease. Quite apart from the temporary effect of acute carditis there may be permanent lengthening of the P–R interval as a result of old rheumatic infection.

Typical examples, all of whom had mitral stenosis, were a woman with a P–R interval between 0·23 and 0·26 sec. during four years; a girl of 8 with a P–R interval of 0·23 sec. for three years; a woman of 55 with a P–R interval of 0·23 sec., who was known to have had this for eight years; a woman of 33 with a P–R interval of 0·23 sec., a large P II, and cyanosis of unusual degree (like Case 45), who died a few months later ; and a man of 29 with a P–R interval of 0·24 sec., who had paroxysmal auricular tachycardia at a rate of 146 without any change in the P–R interval.

As a rule the lengthening was not extreme, but there was one striking exception—a girl with mitral stenosis who was under regular observation for eight years with a P–R interval that increased gradually from 0·26 to 0·36 sec.; apart from tachycardia there was no evidence of any return of active carditis, unless a silent carditis precipitated failure in the last two years of her life (Case 45; see Appendix).

In many of the cases with a long P–R interval due to active rheumatism some slight prolongation had been noticed even before the infection.

There were six patients, who had latent heart block when first seen and later developed auricular fibrillation. One girl with rheumatic aortic incompetence, whose P–R interval had been raised from its normal 0·21 to 0·31 sec. by unwise digitalization during recurrent subacute rheumatism, developed fibrillation four years later. At least three of the others had mitral stenosis; a girl, who had rheumatic fever when 4, had a P–R interval of 0·21 when 10, and fibrillation when 15; a young woman who had a P–R interval of 0·22 sec. during the fifth month of her pregnancy, developed fibrillation after her confinement; and a woman of 37 who had gradually been forced to restrict her very active life, was seen with bronchitis, a P–R interval of 0·24 sec., and a very large P II, and five months later developed fibrillation. No recurrence of active rheumatism was suspected in these last two, but it is, of course, one exciting cause of the onset of fibrillation in some cases.

In addition, two cases first seen with fibrillation had long P–R intervals when normal rhythm was restored with quinidine; in one of these, normal rhythm continued for some years and the P–R

interval was 0·24 sec., so no question of active infection arose. In one man with flutter a long P–R had been enough to produce a heart rate of 72 owing to 4 : 1 block (Case 41, see Appendix), but another in whom the P–R interval was 0·24 sec. had had fairly rapid flutter simulating fibrillation before it was stopped.

In such a mixed group of patients, it is not easy to know the prognosis, and at the time I had not regarded latent heart block as a specially unfavourable sign, perhaps because in those who had done badly there were often other unfavourable signs. Looking through the cases as a whole, it seemed to me they had done less well than might have been expected. The finding of a long P–R interval of 0·24 or above should, therefore, lead to a very careful review of the patient's life and activity and these should be limited until further observation allows gradual progress. No doubt it is partly because latent heart block and large P waves are often found in hearts that are badly damaged in other ways, but it may be that sometimes latent block is a sign of a rheumatic infection that is otherwise silent, and this possibility should be carefully considered.

Myocardial and hyperpietic disease. There seems little special to say about these cases. It was not regarded as a finding of special interest or significance, so no great effort was made to follow them up, but it was often noted that a P–R interval of 0·21–0·24 sec. remained stationary for one or two years. Coronary atheroma (with coronary thrombosis or simple angina), hyperpiesis, congestive heart failure—alone or in combination—or an enlarged heart without evidence of these other factors were all common.

Rarely did any patient, found by chance to have latent heart block, develop complete block. But there were several instances where a patient, sent up because Stokes-Adams attacks or heart block were already suspected had, when examined, latent block only, and later was seen again when he had a higher degree of block. Such cases with 2 : 1 or complete block will be dealt with in a subsequent paper and the relationship of these to latent block will then be discussed more fully. One old man included in this series was sent up with a history of Stokes-Adams attacks and was found to have latent block only (Case 58; see Appendix), but probably if he had been seen more often, complete heart block would have been recorded as he died two years later in another Stokes-Adams attack. In all other instances (unless Case 59 is another exception) such patients were seen at other times with higher grades of block and will therefore be dealt with in the later paper.

Case 55 (Appendix) was of interest, both because of his P–R of 0·35 sec. and because he had anginal pain in a phantom arm.

Case 44 (Appendix) would have been included in the group with no heart disease and the change attributed to his obesity, if he had not been followed up; ten years later the blood pressure was 180/120, but it is possible that this was a coincidence as the P–R interval, though still long, was shorter (Fig. 2).

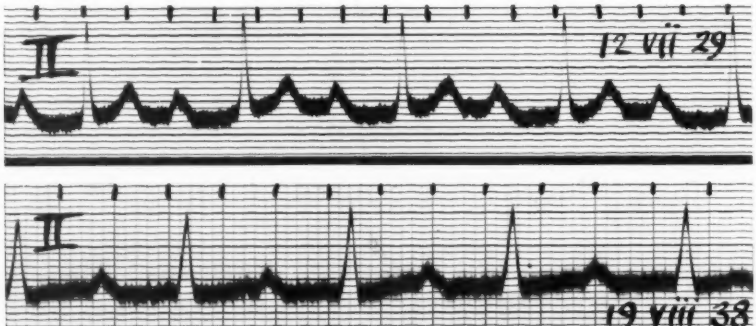

FIG. 2.—Latent heart block with obesity from a man, aged 40, in 1929. Case 44.
(A) 1929, P–R of 0·36 sec. with blood pressure 130/80.
(B) 1938, P–R of 0·31 sec. with blood pressure 180/120.

Bundle branch block. The association of this with latent block was much more common than would be expected if it were a chance coincidence. Apart from the patients with higher grades of block and B.B.Bl., there were 5 of the 141 with latent block who had B.B.Bl. also (2 of the 31 with a P–R interval of 0·26 sec. or above).

This led to my looking through 25 consecutive cases of bundle branch block, excluding any that were already in this series. Sometimes it was not easy to measure P–R, because it was difficult to know where QRS began, and this led to even greater differences than usual between the measurements in the different leads. Using lead II, where it often seemed the longest, the average P–R interval was 0·17 sec.: in 7 it was from 0·12 to 0·15 sec.; in 11 it was from 0·16 to 0·19; in 6 it was 0·20 sec. or a little more; and in 1 only was it as long as 0·24 sec.

Thyrotoxicosis. Nearly one tenth of all the cases with latent block had thyrotoxicosis, but a very large number of thyrotoxic patients were sent for cardiograms. In my own cases where cardiograms had been taken from time to time over a longer period, the P–R interval was not often lengthened without an added infection, so the high proportion may have been due to the large amounts of Lugol's iodine, which many of these patients were taking before operation. This was not the whole explanation, for sometimes it was seen when the patient was not having iodine, and in one case the P–R interval was 0·22 sec. when she was admitted for her first operation and 0·14 sec. six months later, when she was improved but not yet well and was having a second operation: on both occasions she was having Lugol's iodine.

Myxœdema. There were also three cases with latent heart block and myxœdema. In one the P–R interval was 0·23 sec. when there were low-voltage or flat T waves and only 0·20 when the T waves were upright after thyroid treatment. In another the P–R interval was 0·23 without thyroid, and 0·21 six years later when she had again been without thyroid for several weeks. I was surprised at these findings as some years ago in reporting the cardiographic changes in eight cases of myxœdema (Campbell and Suzman, 1934b) comment had been made on the low voltage P that increased with thyroid treatment, but not on the P–R interval. In five of the eight cases there was no significant change. However, three of the eight showed a P–R becoming shorter by about 0·03 sec. after thyroid treatment—0·24 to 0·20 sec., 0·21 to 0·18 sec., and 0·19 to 0·16 sec.—so that this should be added as one of the fairly common features of the myxœdema heart.

Congenital heart disease. Among the cases with latent block there were three examples of this. A girl, aged 13, with coarctation of the aorta and a patent ductus arteriosus, had a P–R interval of 0·26 sec.; she died a year later. A man, aged 28, with bicuspid aortic valves, great enlargement of the heart, and congestive failure had a P–R interval of 0·24 sec.; he died six months later. A woman, aged 35, with moderate enlargement of the heart and an auricular septal defect had a P–R interval of 0·23 sec.; she was alive three years later but was troubled with hæmoptysis.

It seems likely that in all these the latent block was a subsequent development and not part of the original congenital condition, for they were all sick people.

Trauma. There was no cases in this series where latent block seemed to be due to trauma, but such have been reported. One has been added recently by Barber (1942) where a P–R interval of 0·35 sec. persisted for at least five months. Dr. J. R. B. Hern has shown me an example of long P–R, 0·24 sec., following blast from a bomb: though she had orthopnœa and œdema of the legs, the main damage was at first thought to be pulmonary and this was supported by the X-ray findings and the continued cough; however, a year later the P–R interval was still 0·24 sec.

Diphtheria. No cases have been included as diphtheritic. One woman, aged 42, may be mentioned as a possible instance ; seen because of extrasystoles, she had a P–R interval of 0·26 sec. and some cardiac enlargement, and a history of diphtheria as a child (*Case 34*). One girl with a severe relapse of thyrotoxicosis had a P–R interval of 0·22 sec. from the third to the eighth month after diphtheria, but its duration before her attack was not known. A past history of diphtheria has been mentioned in some others (Cases 47, 49, and 55), but in none was there evidence that the prolongation dated from that attack, and it may have represented no more than the expected incidence of past diphtheria in any community.

Bruce Perry (1939) has mentioned two cases of complete heart block persisting for several years after diptheria, but this is certainly rare. Jones and White (1928) investigated 100 patients who had suffered from diphtheria at least five years before; in 70 the attacks had been severe. In no case could they find any evidence that any chronic heart disease had been produced, and on electrocardiographic examination there was nothing more than one example of nodal premature beats with ventricular escape.

Other acute infections. Tonsillitis seemed the most important infection after acute rheumatism. Sometimes it was difficult to be sure that an apparent attack of tonsillitis was not really rheumatic, as illustrated by the following example.

Case 43. A boy of 15, with a doubtful history of growing pains when he was 4, was seen a few days after a sore throat that had followed a 100-mile cycle ride. He was pale and thin, with red tonsils, but no signs in his heart except a P–R interval of 0·26 sec. After his admission to hospital, the sore throat recurred with very little rise of temperature, but he was found to have several rheumatic nodules, and later had one attack of paroxysmal tachycardia. During the month in hospital the P–R interval fell to 0·21 sec.

In spite of this difficulty I feel satisfied that in many cases there were no grounds for suspecting a rheumatic infection. Two have already been quoted where dropped beats and afterwards latent block followed tonsillitis that did not appear to be rheumatic (Cases 5 and 17). The latter has been under observation for 10 years without any evidence to suggest rheumatism, although her P–R interval rose to 0·32 sec. after a transient sore throat, quickly returning to 0·16, at which level it has remained for 10 years. The two patients that follow are further examples without any evidence of rheumatism.

Case 56. A healthy-looking boy, aged 14, came to hospital ten days after an attack of tonsillitis that had lasted three days. He had no history of rheumatism and no symptoms except occasional faintness during the past two years. Nothing was found on examination except a P–R interval of 0·27 sec. and two weeks later this had fallen to 0·21 sec.

Case 59. A boy, aged 18, who had a Stokes-Adams attack three weeks after tonsillitis and came to hospital four days later with a P–R interval of 0·28 (Fig. 3), that quickly fell to 0·16, is reported in the appendix. There was nothing to suggest that the illness was really diphtheria.

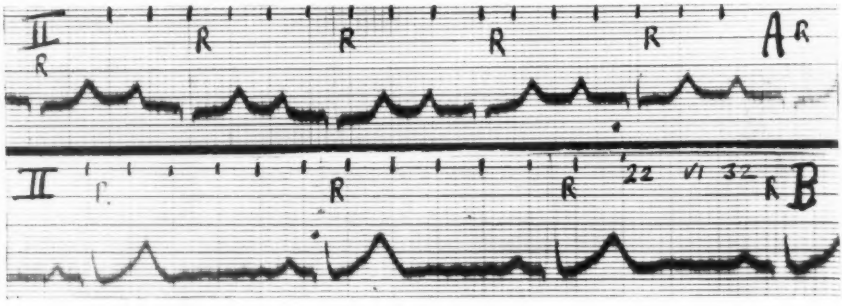

FIG. 3.—Temporary latent heart block after tonsillitis from a young man whose heart was otherwise normal. Case 59.

(A) Lengthened P–R interval, 0·28 sec., three weeks after an attack of tonsillitis and four days after a Stokes-Adams attack.

(B) Rapid return of the P–R interval to normal, 0·16 to 0·17 sec. This curve was taken five weeks after (A), but the P–R interval was 0·18 sec. a week after, and 0·16 to 0·17 two weeks after (A).

Two other patients were included in this group as one was in hospital with a sore throat and the other came up soon after one (Cases 42 and 47; see Appendix). But there was not the same speedy fall of the P–R interval, and follow-up study after 1 and 5 years respectively showed that they still had equally long P–R intervals. This and some other unusual features suggest that the latent heart block may really have preceded their tonsillitis and that they ought to be included as cases without any evidence of heart disease. If so, the range of possible variation in the P–R interval under vagal influence must be considerably widened.

CASES WITH NO APPARENT HEART DISEASE

9 of the 65 cases with a P–R interval between 0·20 and 0·22 sec. were regarded as having no heart disease, though in each case some question had been raised that led to their examination. They were as follows: a girl of 17 with habit spasm and a girl of 19 with obesity; the remainder were men, three being under 40 (31, 28, 27) with pleurisy, an anxiety state, and sinus bradycardia with sinus arrhythmia; three being between 40 and 50 (42, 48, 49) with extrasystoles, vaso-vagal attacks, and a duodenal ulcer; and the ninth, a man of 67 with gallstones. It is possible, of course, that some minor degree of heart disease escaped detection in these cases, but it seems more likely that a P–R interval of 0·21 or even 0·22 sec., though unusual, is not outside the limits of normal.

Case 94. A man, aged 27, who was only seen because of the slow and irregular heart found when he was up for life insurance, was of interest because he was probably an instance of the effect of vagal activity. His heart rate varied between 35 and 48 and his P–R interval was 0·22 sec.

There were 3 of the 45 patients with a P–R interval of from 0·23 to 0·25 sec., who were thought to have normal hearts, and these must be considered in a little more detail.

Case 84. A girl of 21, with a diagnosis of hysterical fits, was sent for examination of her heart because she had twice had chorea, the last time four years before. The P–R interval of 0·24 sec. may have been the result of her attacks of chorea, but nothing abnormal was found about her heart.

Case 72. A man, aged 39, had been under observation for some years with duodenal ulcer and had done well. On one occasion at out-patients, he complained of dyspnœa, and though nothing else was found, his P–R interval was 0·25 sec. On later occasions it had reverted to 0·20 sec., so probably this was due to some transient infection in a heart that was otherwise normal. If so, he should of course be placed in the group with acute infections, but in the absence of more definite evidence it seemed best to discuss him here.

Case 77. A man, aged 50, had fairly severe bronchial asthma of long standing. His heart was thought to be normal but the P–R interval varied between 0·23 and 0·25 sec. It is possible that this may have been the one early sign of heart disease that was not detected otherwise.

In none of these three cases was there any other sign of heart disease.

The main difference between these two groups is that in those with a P–R interval of from 0·20 to 0·22 sec. there was little or no reason for suspecting the heart, while in the group of possible normals with a P–R interval of between 0·23 and 0·25 sec. there was, in every case, some suspicion of early heart disease, though the latent block was the only certain evidence.

One would not expect to find any patients with normal hearts with a P–R interval of 0·26 sec. or more, but three must be mentioned as other evidence of heart disease was trivial or absent.

Case 51. A man, aged 41, was thought to have a normal heart, though at first there was some doubt if the dyspnœa of which he complained might possibly be post-influenzal. In 1931 his P–R interval was 0·24 sec. In 1934 I got him to resume work, and in 1939 his symptoms were much the same and certainly no worse; the P–R interval was 0·27 sec. and records taken most years suggested that this really had been a gradual but irregular increase. His heart was not enlarged and there was no other evidence of disease.

It is of interest because it is possible that it represents a slight progressive change that in the course of several more years will result in a higher grade of heart block recognizable clinically. But this course is unlikely for many of these cases have been followed for years, and such changes have been looked for and yet we have no other similar example.

Case 40. Here, the interpretation is difficult. In 1927, when 43, he was thought to have a P–R interval of 0·35 sec. (Fig. 4). He complained of extrasystoles, paroxysmal tachycadria, and symptoms that were due to anxiety. He was seen at intervals during the next ten years, and never had any symptoms suggesting heart disease, nor a P–R interval longer than 0·16 sec. He was not taking any drug known to affect the heart at the time the long interval was observed.

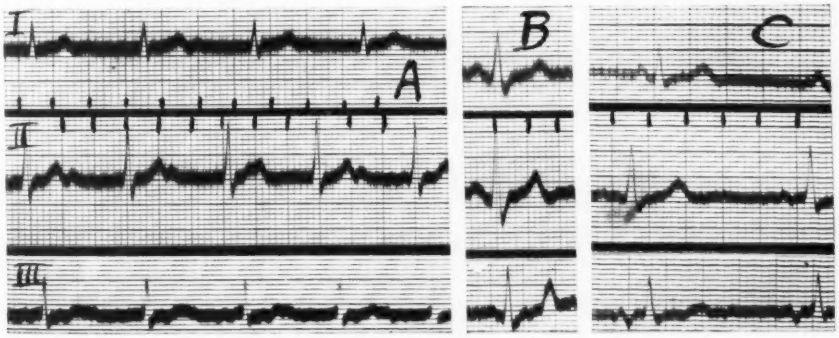

FIG. 4.—Temporary latent heart block of high grade. Case 40.
(A) Cardiogram of 1927, with a P–R interval of 0·35 sec. No other explanation seems possible, especially in view of the fourth response in lead II being premature, but still with the same P–R interval.
(B) A week later, and (C) ten years later, both these showing a normal P–R intervals of 0·16 sec.

It is possible that this was an unusual result of a minor transient infection; although an extreme example it would not be much more extreme than some others.

Case 49. A man, aged 28, was sent for a cardiogram because of extrasystoles. The diagnosis of tuberculosis of the lungs was considered but not proved, for though he complained of cough and loss of weight, the X-ray was inconclusive. His heart was thought to be normal except for the extrasystoles, which sometimes after exercise were so frequent as to simulate paroxysmal auricular fibrillation, and a variable P–R interval which changed from 0·20 to as long as 0·36 sec. There was no gradual increase, but on two occasions where records were obtained (and as far as could be judged on several other occasions) there was suddenly a very long P–R interval up to 0·36 sec. with the P-P interval remaining constant, and the R-R interval lengthening appreciably (Fig. 5). Such a

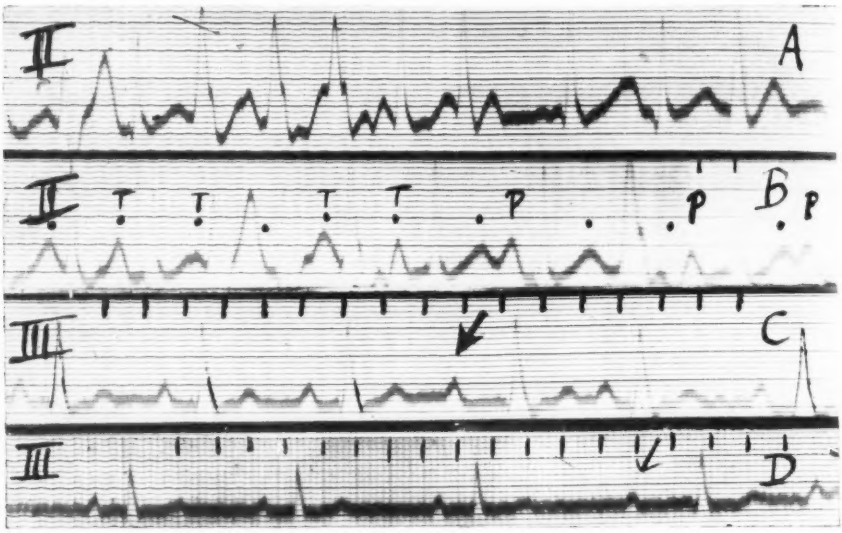

FIG. 5.—Irregular latent heart block of high grade. Case 49.

(A) and (B) Irregular rhythm after exercise.
(C) April 1935 and (D) June 1935, showing single P–R intervals of 0·36 sec., interrupting P–R intervals of 0·20 sec. These are probably vagal effects in a normal heart.

sudden change must almost certainly be a vagal effect and related to sinus arrhythmia, but it is curious that even so it should not occur more gradually. Nor was there any sinus bradycardia such as has been described in Case 94 with much less lengthening of the P–R interval. After eight years he was written for and seen again. He had been getting on well and had been working regularly, with no symptoms. His heart rate was 80 with much irregularity after exercise; this seemed to be (*a*) an extreme sinus arrhythmia, the rate doubling, but not suddenly as with S-A block, and at times; (*b*) a gross irregularity that was not influenced by respiration and lasted for some beats only. X-ray confirmed that there was no enlargement of the heart and showed some old calcified areas below the right clavicle.

Cases 42 and 47 in the appendix should be noted in this connection; at the time the latent block was thought to be the result of attacks of tonsillitis, but its persistence and some other features suggest that in these two as well as in *Case 49* it may really have been an unusual vagal effect.

THE LENGTH OF THE P–R INTERVAL

As would be expected, P–R intervals a little above the normal are very much more common than those greatly above it. There were a large but diminishing number at each hundredth of a second from 0·21 to 0·24, a moderate but more slowly diminishing number at from 0·25 to 0·28, and a smaller and fairly steady number (at each hundredth of a second) from 0·29 to 0·37 sec. Those with P–R intervals of 0·21 and 0·22 and those with P–R intervals of 0·23 and 0·24 have been combined, and so on, partly because the numbers were small and partly because there was a little tendency to record the measurements by even numbers. The full figures are shown in the second column of Table III.

TABLE III

LENGTH OF THE P–R INTERVAL

Length of P–R interval in seconds	Number of cases			
	(IV) Latent heart block only	(III) Dropped beats and, at other times, latent block	(II) Complete or 2 : 1 block and, at other times, latent block	Total
Less than 0·20 sec.	—	2	5	7
0·21 0·22	65	4	5	74
0·23 0·24	39	1	6	46
0·25 0·26	13	3	3	19
0·27 0·28	8	6	1	15
0·29 0·30	2	3	2	7
0·31 0·32	4	4	1	9
0·33 0·34	3	2	2	7
0·35 0·36	4	1	0	5
0·37 0·38	2	0	0	2
0·39 0·40	1	1	0	2
0·44	—	0	1	1
0·47	—	1	—	1
0·56	—	1	—	1
Total number	141	29	26	196
Average P–R interval ..	0·24 sec.	0·28 sec.	0·25 sec.	

A smoothed curve has been drawn in Fig. 6. It falls very sharply at first between 0·24 and 0·25, but then levels out and shows little further tendency to fall after 0·29 until it practically comes to an end at 0·40 sec., above which there were only single cases.

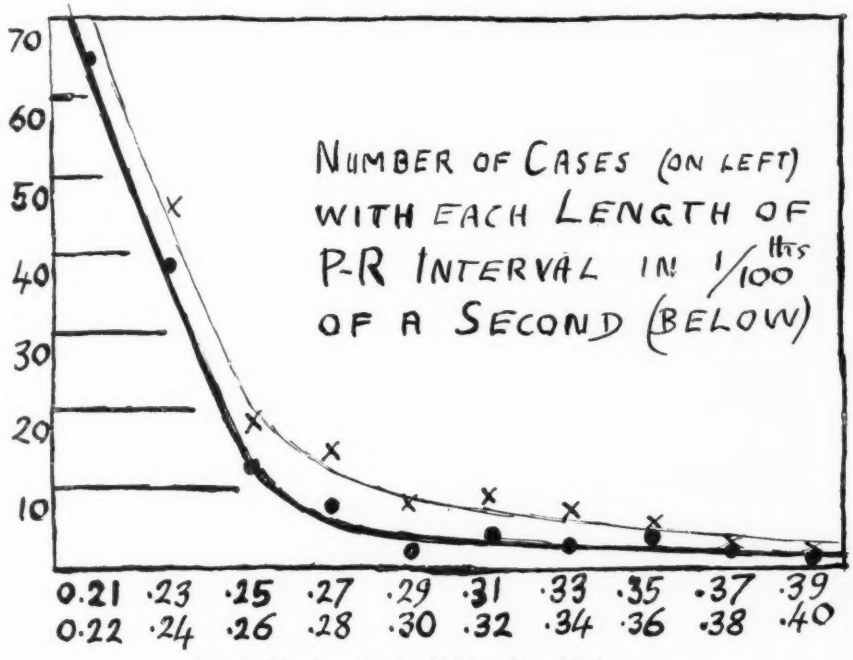
70
60
50
40
30
20
10
NUMBER OF CASES (ON LEFT) WITH EACH LENGTH OF P-R INTERVAL IN 1/100ths OF A SECOND (BELOW)
0.21 0.22 .23 .24 .25 .26 .27 .28 .29 .30 .31 .32 .33 .34 .35 .36 .37 .38 .39 .40

FIG. 6.—Number of cases with latent heart block.

Abscissæ, length of the P–R interval in hundredths of a second; ordinates, number of cases.
The thick line below includes the 141 cases with latent heart block only.
The lighter line above includes the additional 53 cases that had dropped beats or higher grades of heart block at one time and latent block only.

There were 141 cases with heart block that was latent only; 29 others had sometimes dropped beats and sometimes latent block; and another 26 had sometimes 2 : 1 and/or complete heart block and sometimes latent block. One might expect in each of these groups also, either that the frequency distribution would be similar or possibly that the length of the P–R interval would vary round a much higher average figure.

This was not so; in those with latent heart block only, 74 per cent of the cases had a P–R interval of 0·24 sec. or less (46 per cent, 0·21 or 0·22); in those with dropped beats, only 24 per cent had a P–R interval of 0·24 or less, and 65 per cent had figures of 0·27 sec. or above; those with 2 : 1 and/or complete heart block also, was more like the former than the latter, 61 per cent having a P–R interval of 0·24 or less, but being more equally distributed through the range.

In those with latent block, the average P–R interval was 0·24 sec. and most of the cases were between 0·21 and 0·24 sec. In those with dropped beats, the average was much higher, 0·28, and most of the cases (55 per cent) were between 0·27 and 0·34 sec. In those who had at times higher grades of heart block the average was intermediate and nearer to that of latent block, viz. 0·25, with a range more equally distributed between 0·19 and 0·26 sec.

The full figures have been given in Table III. Table IV shows certain statistical data which may make the results clearer to some. The median is the point above and below which there are equal numbers of cases; the mode is the point at which the largest number of cases are grouped: if the distribution curve was symmetrical these two figures would of course be the same as the average, but with such a skew distribution curve for latent heart block there is much divergence; in the other two groups the divergence is much less.

TABLE IV

AVERAGE AND MEDIAN P–R INTERVALS IN DIFFERENT GRADES OF HEART BLOCK

	P–R intervals (in seconds) in latent heart block		
	(IV) Latent block only	(III) With, at other times, dropped beats	(II) With, at other times, 2 : 1 or complete block
Average	0·239	0·278	0·254
Median	0·226	0·283	0·240
Mode	0·21	0·28	0·24
Quantiles	0·210–0·244	0·246–0·322	0·215–0·270
Usual range	0·21–0·24	0·27–0·32	0·19–0·26

The quantiles give the points between which half the cases lie; one-quarter being outside and above, and one-quarter outside and below. The usual range was chosen by inspection (before the quantiles were known) and has no exact mathematical meaning. It has been thought worth giving these additional figures because with such a wide range of variation average figures alone give a very imperfect picture.

CASES WITH THE LONGEST P–R INTERVALS

The ætiology of latent heart block in general has been discussed; in this section those with the longer P–R intervals will be considered in more detail.

Of the 31 cases where it was 0·26 sec. or above, 11 had rheumatic heart disease. They were on the whole young but not very young patients, at an age still liable to acute rheumatism rather than at the age most prone to suffer from the late results of old rheumatic heart disease. Only one was over 27 and the average age was just under 24 years. In 4 of the 11 the lengthening was transient and certainly due to an acute infection; in 3 it was transient and probably due to an acute infection (though in both these groups there was often a slightly

prolonged P–R interval before and/or after the transient increase); and in 4 it was persistent and not due to any active infection.

There were 12 of the 31 with myocardial disease, generally coronary atheroma or high blood pressure. They were, as might be expected, older patients, the average age being 58 and only three being under 50 years of age. The only two in whom the heart disease was not gross and obvious were *Case 34* (see p. 169) and *Case 44* who had developed high blood pressure after 10 years, but might have been described as normal as nothing was found at fault except his obesity and latent block (see p. 168).

One case had congenital heart disease (*Case 37*, see p. 169).

This left 7 cases where the heart was thought to be free from any organic disease. They were mostly young adults with an average age of 26 years. In 3 of the 7 no cause was found (*Cases 40, 49, and 51*; see p. 171). In the other 4 the long P–R interval were thought to be due to an attack of tonsillitis without any evidence that this was rheumatic. In 2 of these 4 the lengthened P–R disappeared quickly, confirming this view (*Cases 56 and 59*, see p. 170); but in 2, a recent follow-up has shown that it has persisted for 1 and 5 years respectively, and other features, the extreme sinus arrhythmia and the P–R interval of either about 0·36 or about 0·24 sec. suggest that possibly the attacks of tonsillitis were not the cause and that these were unusually marked effects of vagal activity (*Cases 42 and 47*, see p. 179).

This gives a very different picture, clinically and ætiologically, from that found with the higher grades of heart block. This is confirmed even by the most cursory glance at Table V. Here the 15 cases with a P–R interval of 0·30 sec. or more are shown: 9 were between

TABLE V

CLINICAL NOTES OF CASES WITH A P–R INTERVAL ABOVE 0·30 SEC.

Case No.	Sex and Age when first seen	Years under observation	P–R interval		Diagnosis of heart condition	Remarks
			longest	shortest		
45	f. 15	7	0·40	0·26	Rh. mitral stenosis	Lengthened by digitalis, but finally 0·36 without it.
49	m. 28	8	0·37	0·20	Normal	Extrasystoles and tuberculosis.
58	m. 77	3	0·37	—	B.P. 280/100	Stokes-Adams attacks; died after 3 years.
44	m. 40	9	0·36	0·31	Obesity	1919: obesity, B.P. 130/80; 1938: B.P. 180/120.
47	m. 20	1	0·36	0·24	Normal	Recent sore throat; ? incidental.
40	m. 43	10	0·35	0·16	Normal	Long P–R once only.
55	m. 52	1	0·35	0·35	Myocardial	Coronary atheroma; ? recent infarction.
57	m. 54	—	0·34	0·26	Rh. mitral stenosis	Congestive failure: increased by digitalis.
35	f. 24	1	0·34	0·14	Rh. aortic incompetence	? Rheumatic carditis but no other evidence.
42	f. 21	6	0·33	0·28	Normal	Recent sore throat when first detected.
50	f. 25	2	0·32	0·25	Rh. mitral st.	Recurrent carditis.
54	m. 24	—	0·32	0·19	Rh. mitral st.	During rheumatic fever.
48	f. 18	5	0·31	0·20	Rh. aortic incompetence	Mainly due to digitalis, but also recurrent rheumatism.
36	m. 14	6	0·31	0·21	Rh. mitral and aortic	Lengthened during terminal attack of rheumatic fever.
41	m. 68	2	0·30	0·25	Myocardial	Flutter with 4 : 1 block; digitalis restored N.R.

14 and 25 years of age; 7 had rheumatic valvular disease; 4 (or 5 if Case 44 be included) were thought to have hearts that were free from organic disease, though 2 gave a history of sore throats; and only 3 were elderly men with signs of cardiac disease, such as are generally found with complete heart block.

There were also 12 cases, described in the paper as partial heart block with dropped beats (Campbell, 1943; most are listed in Table II on p. 56) who had at other times latent block only, with a P–R interval of 0·30 sec. or more. As a group they resemble the cases just described very closely: 8 were between 18 and 30 years of age; 5 had rheumatic heart disease; 5 were thought to be free from organic heart disease, but acute infections seemed a rather more important factor here; and only 2 were elderly patients (and in one of these the block was due to digitalis). In both these groups efforts have been made to keep in touch with most of the patients for many years, and only one has gone on to complete heart block (Case 58). Often the long latent block fell to a less prolonged figure (say, 0·21 to 0·25), but sometimes it persisted.

The patients with the highest grades of latent block are therefore a rather special group. In some, acute infections are the cause and the block is temporary; in others, the reason is obscure, and in some of these there seems little else the matter with the heart.

Summary and Conclusion

Latent heart block is a convenient term for a conduction time that is prolonged without any dropped beats or higher degree of block.

All those where the P–R interval was above 0·20 sec. have been included in this series. About 2 per cent of the patients sent to a cardiographic department showed this change, and 141 cases were analysed. The incidence fell very rapidly from 0·21 to between 0·24 and 0·25 sec., and then more slowly to 0·29, after which it was steadier, cases being seen at all levels up to 0·40 sec.; longer P–R intervals than this were very rare. In nearly half (46 per cent), the P–R interval was not more than 0·22 sec. In nearly one-quarter (22 per cent), it was 0·26 sec. or more.

In addition, 29 cases, which sometimes had dropped beats and sometimes latent block only, and another 27, which sometimes had 2 : 1 and/or complete heart block and sometimes latent block only, were analysed.

When there was latent block only, the P–R interval was most commonly between 0·21 and 0·24 sec. When latent block interrupted complete and/or 2 : 1 block the figure was much the same with a rather wider common range, 0·19 to 0·26 sec. On the other hand, when there were at times dropped beats, and at other times latent block only, the P–R interval was on the average longer, and was generally from 0·26–0·32 sec., possibly because more of these cases were due to a transient acute infection.

As a rule, latent block did not progress to higher grades of heart block. In many it diminished as the effect of an acute infection disappeared; in some it remained at a fairly constant level; and in some it was found, occasionally or from time to time interrupting complete and/or 2 : 1 heart block.

The ætiology varied somewhat in the different groups. Where the P–R interval was from 0·20 to 0·25 sec., all types of heart disease were represented in much the same proportions as might be found in any collection of cardiac cases.

Where the P–R interval was 0·26 or above, the ætiology was more like that found in cases with dropped beats: 41 per cent (as against 11 per cent with a P–R interval from 0·20 to 0·25 sec.) had acute rheumatism or other active infections, mostly tonsillitis, and there were fewer cases with thyrotoxic or normal hearts.

Cases with latent block and at other times 2 : 1 or complete block were ætiologically like the cases with complete heart block, i.e. older patients with atheroslcerosis or primary myocardial disease (69 per cent against 26 per cent in the two previous groups, or 86 per cent against 39 per cent if hyperpietic cases were included).

Acute rheumatic carditis was a common cause of P–R intervals that were much prolonged, to 0·26 sec. or above. Chronic rheumatic heart disease occasionally caused these longer

values, but was more often responsible for the slighter increases from 0·20 to 0·24 sec. Other acute infections sometimes produced quite a long P–R for a time; these including attacks of tonsillitis that were almost certainly not rheumatic.

Latent heart block, especially of the lesser grades, was seen in all types of chronic myocardial disease. Even here it seemed rare for it to progress gradually to complete heart block, though often it interrupted complete or 2 : 1 block, sometimes after surprisingly long intervals.

Both in thyrotoxicosis and myxœdema, long P–R intervals were observed, and the relationship of this to iodine therapy in thyrotoxicosis needs more investigation.

No instances of latent block due to trauma were included in the series, though such cases have been reported; and one due to blast has been mentioned.

There were no cases where latent block could with certainty be attributed to diphtheria, but such a history was noted in some cases as a possible cause that could not be excluded.

Some curious cases have been described in which P–R intervals, even up to 0·30 sec. or more, were found without any other evidence of heart disease. As some of these persisted they did not seem to be due to infection, and it is suggested that exceptionally overaction of the vagus may produce unusually long P–R intervals. In some, which have been described rather fully, the longest P–R intervals were irregular or intermittent.

Some few cases with a P–R interval up to 0·22 sec. or even higher seemed to be normal in every way.

Appendix of Case Notes

Cases with Acute Rheumatism

Some typical cases have been referred to in the text (p. 167) and in a previous paper (Campbell, 1943, p. 56). A less usual case is added below.

Case 35. C., aged 24, complained that she had fainted after a hot bath; probably her doctor would not have sent her to hospital had he not found a murmur. She had free aortic regurgitation with some enlargement of the heart, and though there was no rheumatic history slight mitral stenosis confirmed that it was rheumatic. Her attack seemed like an ordinary faint and had none of the characteristics of a Stokes-Adams attack so that a P–R interval of 0·34 sec. was a surprise. We expected this would prove to be a permanent feature of her heart, but she was told to lead an easy life and return in two weeks in case a change should show there had been active carditis.

She resumed her normal life and was not seen again till she was written for after six months. She had no symptoms except the slight degree of dyspnœa to which she was accustomed. Her P–R interval was now 0·14 sec. This gives an important indication of the changes that may be going on in the heart unsuspected, and means that even in the young an attack of faintness may occasionally indicate cardiac damage.

Cases with Chronic Rheumatic Heart Disease

Several of these have been quoted shortly in the text, and the following is given in more detail because of the unusual length of the P–R interval.

Case 45. I. J. had chorea and rheumatism at 11, and four years later (1932) was found to have enlargement of the heart (13 cm./22 cm.) and high-grade mitral stenosis. She complained of cough and dyspnœa and was unusually cyanosed. The P–R interval was prolonged, and on 12 occasions during the next year it varied between 0·24 and 0·28 sec. Her heart rate was generally 108–120, but there was no other evidence of recurrent rheumatism.

During the next two years, treatment with digitalis improved her condition as regards her dyspnœa and cyanosis, but the heart rate remained about 96–108. It lengthened the P–R interval to between 0·32 and 0·40 sec. Although she was seen nearly every fortnight during three years no dropped beat was ever observed (Campbell, 1942, p. 140).

In 1934 she started work and was seen less regularly. In 1936 some œdema of the feet developed and she began having short paroxysms of tachycardia, lasting up to half an hour. She was never quite so well after this, but continued at easy work with short periods in hospital for another two years. The P–R interval varied between 0·32–0·36 sec. and was often this length when she was not taking digitalis. She was lost sight of after December 1937, and died elsewhere in February 1939 and we have not been able to get details of her final illness.

Here a P–R interval of 0·28–0·36 sec. persisted for at least 7 years, and even when she was taking digitalis no dropped beats were ever observed.

Cases with Myocardial Disease

Case 41. *Latent block, producing spontaneous* 4 : 1 *block when there was auricular flutter.*

A man, aged 68, with a large heart and a blood pressure of 160/100 came to hospital, complaining of cough and dyspnœa. His pulse rate was 76, but this was found to be due to auricular flutter with spontaneous 4 : 1 block, which after exercise changed to irregular 2 : 1 block. He was given Nativelle's digitaline, and when he came to hospital a fortnight later said he had taken 1/600 grain t.i.d. the first week, and q.i.d. the second week. This had restored normal rhythm and the P–R interval was 0·30 sec., compared with his normal of 0·24, which was found during the months following when he was not taking digitalis. In this case the latent heart block was as helpful as digitalis treatment would have been in producing such a degree of block that the ventricular rate was normal as long as he was not exerting himself.

This is not uncommon with auricular fibrillation where some natural degree of block in an elderly patient helps in the same way that digitalis would by reducing the ventricular rate; but with fibrillation it cannot be demonstrated so elegantly as in this case of flutter.

Case 44. *Latent block and obesity, followed after some years by high blood pressure.*

A man, aged 40, was admitted to hospital for fatigue, dyspnœa, and headaches, the latter due to severe myopia in the right eye. All his symptoms were attributed to his excessive weight of 16 stone, and nothing else abnormal was found except a P–R interval of 0·34–0·36 sec. (Fig. 2). The Wassermann reaction was negative. He improved with thyroid and dieting.

Two years later his condition was somewhat better as he had kept his weight lower, but the P–R interval was still 0·36 sec. He had taken no thyroid for some time as it upset him, but had restricted his diet.

After another eight years he was re-admitted for increasing dyspnœa. He had never felt well but he had been at work all the time and had kept his weight to 15 stone by eating very little except bread and butter. The P–R interval was 0·31 sec. and the blood pressure, which had been 130/80 in 1929 and 145/95 in 1931, had risen to 180/120; the first sound was reduplicated. No other abnormality was found, except that the cardiogram now showed flat T waves as well as the latent heart block.

Case 55. *Latent block and angina, with anginal pain felt in a phantom arm.*

One of these patients is of interest, not only because of his long P–R, 0·35, but because he had anginal pain in a phantom arm. His right arm was blown off in France in 1917. Eighteen years later, in May 1935, he began having anginal pain which started across the chest and spread down the right phantom arm with great regularity. In October 1935 his pain became worse and he may have had a cardiac infarct, but there was no cardiographic proof of this. In May 1936, when he was 52, he came to hospital as his angina was troublesome and persistent. Nothing was found on examination except a P–R interval of 0·35 sec. which remained constant for the three months he was under observation. He had had diphtheria in 1933.

We were much interested in the pain he felt in his phantom arm because of its occurrence so long after the loss of his arm, but not surprised as it seemed to us that with a pain that was normally referred from the centre to the arm, it must still be felt there if the arm was able to give rise to sensations of any sort: we did not realize till seeing the paper by Cohen and Wallace Jones (1943) that such a case had not been reported. Dr. S. Suzman made many attempts to study his reaction to nitrites, but it was not easy to provoke the pain by any exercise he took while under observation as the onset was less regular than in most cases of angina.

Case 58. *Stokes-Adams attacks: latent block only while under observation.*

A fine, healthy-looking old seaman, aged 76, had a Stokes-Adams attack. He had no other complaints except a little dyspnœa. A year later, although he had no more attacks, he was sent to hospital and the cardiogram showed a P–R interval of 0·37 sec. He gave a clear account of his pulse getting slower with more dropped beats, and stated that the pulse rate often fell to 33, especially in bed in the morning, so that it is almost certain he had complete or 2 : 1 heart block. His heart was enlarged, his blood pressure 280/100, and the Wassermann reaction positive. He was not seen again and died suddenly three years later.

Cases with Tonsillitis

Case 5 and *Case 17* have been reported already (Campbell, 1943, p. 57) as at one stage they had partial heart block with dropped beats, but are pertinent here as at a later stage they had latent heart block only.

Case 59. S. S., aged 18, had tonsillitis, a first attack, and was at home for a week without seeing his doctor. He returned to work but did not feel as well as usual. After two weeks at work he woke up feeling sick, and on his way to the lavatory fell down unconscious and cut his face severely. His doctor found his pulse rate 34, and kept him in bed till he came to hospital four days later

Nothing was found abnormal except an altered first sound, slight albuminuria, and a P–R interval of 0·28 sec. (Fig. 3A); a week later this was 0·18, and after another week 0·16 sec. (Fig. 3B). He felt quite well and continued at work. It seems unlikely that this was an undiagnosed attack of diphtheria.

If he had not been seen again this would seem a simple case where the P–R interval was lengthened by tonsillitis and where there had been complete heart block with a Stokes-Adams attack, his recovery being complete and rapid. But nine months later when asked to come to hospital again he had a curious cardiogram. He had been quite well until " influenza " a month before and had had no more attacks of faintness or loss of consciousness. The usual P–R interval was now 0·23 sec., but sometimes it was much shorter as though there was ventricular escape (R_4 in Fig. 7D and to a lesser extent

FIG. 7.—Sinus arrhythmia with variation of the P–R interval, which is at times much below its usual length of 0·23 sec., probably due to ventricular escape. From the same Case 59 as Fig. 3, all taken nine months later (17/2/33), shortly after an attack of influenza.

(A) Ventricular escape (see text).
(B) Shorter P–R interval after a pause in the sinus rhythm.
(C) Ventricular escape (R1), nearer to the auricular wave than in (A).
(D) Sinus arrhythmia with ventricular escape twice during the slower period.

R_6 of Fig. 7B). Sometimes this happened where there was a longer pause, probably during the expiratory phase of sinus arrhythmia. Sometimes, however, it happened without any sinus arrhythmia (see Fig. 7A): there the P-P intervals were constant, but the R-R intervals were shorter so that the first four P–R intervals became shorter or non-existent, until the fifth R-R interval being longer allowed P–R to reappear; nodal rhythm arising in different sites could explain this, but the regular P-P rate makes this unlikely, and frequent ventricular escape at a rather rapid rate seems the most likely explanation.

Cases with Tonsillitis that may have been merely incidental, in which event they should be included as Cases with no other evidence of organic heart disease. Cases with no other evidence of heart disease have been described in the text (pp. 170–172).

Case 42. A nurse, aged 21, was admitted with a sore throat, a temperature of 102, and a pulse rate of 80. The third day she felt well and her temperature was normal, but her heart rate was found to be irregular and about 50. Dropped beats were suspected and two days later the P–R interval was 0·29–0·32 sec. (Fig. 8). A week later it was unchanged, and three weeks after when she had been feeling perfectly well, a record was obtained that was at first thought to be dropped beats but was sino-auricular block or perhaps extreme sinus arrhythmia as the long P-P interval was much less than twice the normal: no progressive lengthening of the P–R interval of 0·32 sec. was observed. A week later when she was allowed up, P–R was again 0·30 sec. and regular.

She was not seen again for two months as she was on holiday, feeling quite well. Four months after the sore throat that had lasted only two days, sino-auricular block or extreme sinus arrhythmia with other periods regular was again observed, with the P–R interval unchanged; in the absence of symptoms or other signs she was allowed to resume work.

After another year, during which she had continued at work, she felt well and showed no physical signs, except that P–R was still 0·30 sec. She gave no history of rheumatism at any time. It was at that time thought unlikely that she had any degree of heart block before her short illness.

During the next four years she carried out her work as a nurse without any symptoms or disability,

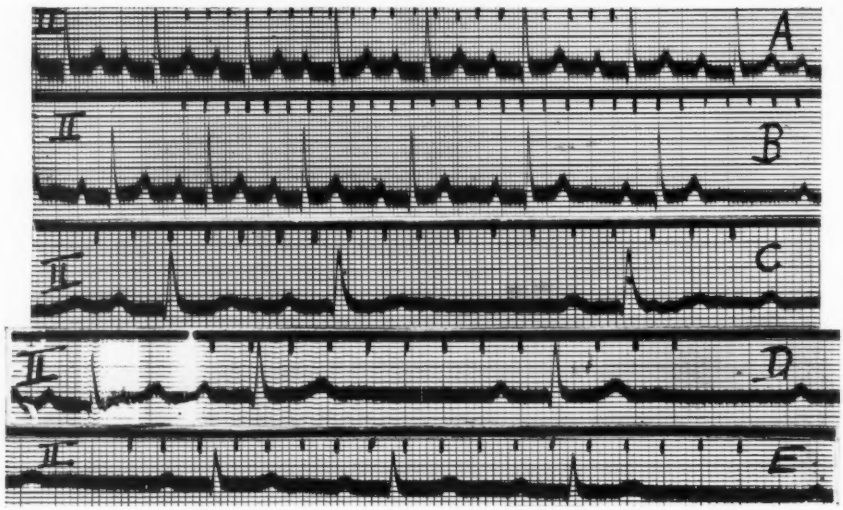

FIG. 8.—Extreme sinus arrhythmia with a long P–R interval, persisting for at least five years. Case 42.
(A) The most usual finding with a rate that is nearly regular (shortest R–R, 0·86; longest R–R, 0·96).
(B) On the same date, changing to a much slower rate—the six P–P's being 0·92, 0·92, 1·02, 1·07, 1·18, and 1·54 sec. (C), (D), and (E) all show marked sinus arrhythmia, the last two being taken during deeper respiration.
(C) Was taken on 14/2/38, three weeks after a sore throat (which may have been incidental); all the others were taken on 2/3/39.
In 1943 the P–R interval was still 0·31; the rate was regular when recorded, though at other times there was some irregularity that did not appear to be associated with respiration.

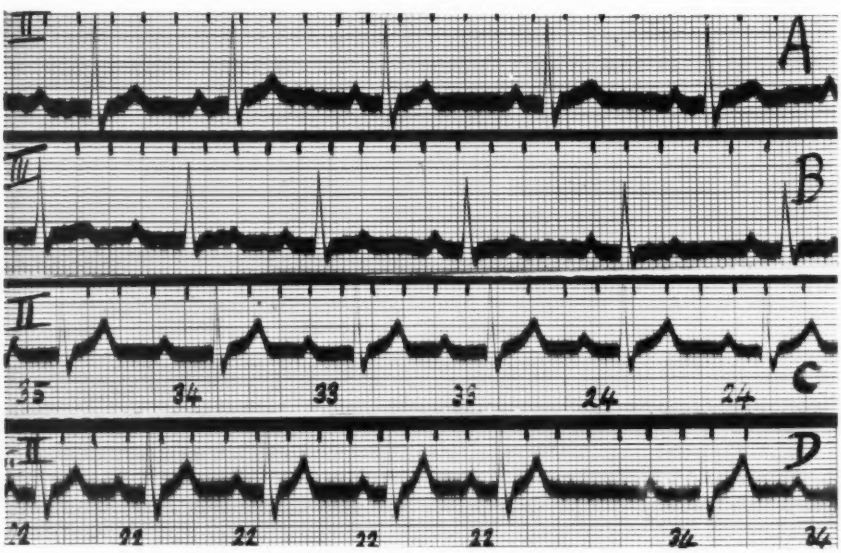

FIG. 9.—Changes of long and shorter P–R intervals. Case 47; see also Fig. 1.
(A) and (B) Both show the change from the long to the shorter P–R interval at the beginning of the picture (5/6/39.)
(C) Shows better the change from the long to the shorter P–R interval; the P–P intervals are nearly constant, but shorten a little from 0·96 to 0·87 sec. (26/6/39.)
(D) Shows the change from the shorter to the long P–R interval; the last P–P interval before the long P–R is much longer than usual (but not twice as long); as a rule, however, the rate of the heart with the long or with the shorter P–R interval was the same. (26/6/39.)

leading a normal life in every way. Nevertheless, her P–R interval was still 0·31 sec. as it had been four years before. Her heart rate was between 56 and 64 with some slight irregularity of the sinus type that was not, however, associated with respiration. There were no abnormal physical signs.

At first she was thought to be a case of partial heart block following tonsillitis as in the two cases described with dropped beats (Cases 5 and 17), one of these also being a nurse; but its long persistence without any other symptoms and the association with sinus arrhythmia that was at times extreme enough to simulate sino-auricular block suggests that it may be a physiological, though unusual finding in a patient with very high vagal tone.

Case 47. A young man, aged 20, came to hospital complaining of breathlessness and pain in the left side of the chest which had been present most days for a year. He was anxious about tuberculosis as he had a bad family history, but clinically and on X-ray examination his chest was normal. He was liable to sore throats and had been ill with this three weeks before for four days, but had not seen his doctor as it seemed no worse than usual. He had fainted once nine months before. He gave no history of rheumatism, but had had diphtheria as a child.

Nothing was found on examination except that his P–R interval was about 0·24 sec. For this reason only he was asked to return the following week, when his P–R interval was sometimes 0·24 and sometimes 0·34 sec. This was observed on many occasions during the next nine months, the longer P–R interval always being between 0·32 and 0·36, and the shorter always between 0·22 and 0·26 sec. On one occasion only he was seen with a heart rate nearly 100 and the interval was as short as 0·20 sec.

Generally the rate was relatively slow, about 60, and sometimes as slow as 44. There was no general difference in the heart rate whether the P–R interval was about 0·24 or about 0·34 sec., the average rate in both cases being 61. On one occasion (see Fig. 9D) there was a change to the long P–R interval after a pause and perhaps with a slower rate afterwards, but on the same day another plate showed the reverse change without any change of rate (see Fig. 9C). Most often, all the beats in one lead showed the same P–R interval, but records showing the change over have been picked out for illustration.

During the year he was under observation there was no regular change in his symptoms, which were sometimes better and sometimes worse. His sedimentation rate was normal; an X-ray of his chest was clear; and the throat surgeon reported that though he had frequent slight attacks of tonsillitis there was no focal sepsis. He was not unduly thin and was putting on weight.

At first the long P–R interval was attributed to his recent tonsillitis, but the relatively slow heart with the variable P–R interval suggest a high degree of vagal tone, and it is possible that this was usual with him and quite independent of the recent attack. Attempts to trace him recently have not been successful.

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